From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT MRI study
Date: Friday, December 23, 2005 12:17:34 PM

Hi again,

Who should I ask from RTI to send another email re: how many sites plan to get/have gotten IRB approval for the secondary? Let me know if you think the following questions would give the information we need:

1) Has your site received IRB approval for the SUPPORT Neuroimaging secondary?
    a) If so, will your site be using a separate consent for the Neuroimaging secondary, or will the consent be embedded in the overall study consent?

2) If your site has not received IRB approval, has your site applied for IRB approval for the SUPPORT Neuroimaging secondary?
    a) If not, does your site intend to participate in the SUPPORT Neuroimaging secondary?

Thanks -

Susan
--
Susan R. Hintz, M.D.
Assistant Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Poole, W. Kenneth
Subject: SUPPORT DSMC
Date: Tuesday, December 20, 2005 2:29:17 PM

Rose:

I discussed with Marie your idea about using the face-to-face DSMC meeting to present interim monitoring data as well. It seems that, as far as efficacy is concerned, the first formal look is at 25% which would be 320 babies. Since we only have 243 enrolled, we're not there yet. However, we can share the latest safety looks with them (we do that roughly after every 60 babies).

Thanks

Abhik

Abhik Das, Ph.D.
Senior Research Statistician

RTI International
6110 Executive Blvd., Suite 902
Rockville, MD 20852-3903
e-mail: adas@rti.org
Phone: 301-770-8214
Fax: 301-230-4646

From: Wally Carlo, M.D.
To: nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: DSMC
Date: Tuesday, December 20, 2005 11:56:18 AM

Neil. Thanks a lot. Happy Holidays.
Wally
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
CC: 'Higgins, Rosemary (NIH/NICHD)' <higginsr@mail.nih.gov>
Sent: Tue Dec 20 10:48:21 2005
Subject: RE: DSMC

Hi Wally

It will be good to have you at this meeting. Thanks for agreeing to participate.

I am attaching the latest PowerPoint. I know that you are traveling so have a look at it when you get home.

All the best for the Holidays

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, December 20, 2005 8:34 AM
To: higginsr@mail.nih.gov
Cc: nfiner@ucsd.edu
Subject: Re: DSMC

Dear Rose:

Sure. I will do it.

(b) (6) Is it? We love it.

Wally
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
CC: nfiner@ucsd.edu <nfiner@ucsd.edu>

Sent: Tue Dec 20 10:26:07 2005
Subject: DSMC

Hi Wally,

I understand you are on vacation and really hate to bother you; however, I have an important request. I think it would be good if you could attend the open portion of the DSMC meeting on the SUPPORT trial as you are the most active member of the subcommittee next to Neil. The meeting is possibly going to occur on January 24 in Rockville at the RTI offices. Let me know if this is a possibility.

Since you (b) (6) (if you have time)!!
Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Neil Finer
To: "Wally Carlo, M.D."
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: DSMC
Date: Tuesday, December 20, 2005 11:49:46 AM
Attachments: SUPPORT Trial Final DSMC Response - Dec 17.ppt

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I am attaching the latest PowerPoint. I know that you are traveling so have a look at it when you get home.
All the best for the Holidays
Neil

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To: higginsr@mail.nih.gov
Cc: nfiner@ucsd.edu
Subject: Re: DSMC

Dear Rose:

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(b) (6) [redacted]. Is it? We love it.

Wally
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
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To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
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Since you are (b) (6) [redacted] (if you have time)!!
Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

December 11 2005

Report of the DSMC Nov 2005

The DSMC expressed 2 concerns:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

Report of the DSMC Nov 2005

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Evidence for Current SpO2 Ranges

- **SUPPORT Trial alarm limits were chosen as those most currently utilized within the Network and consistent with current evidence.**
- **To maintain PaO2 between 40 and 90mmHg would require SpO2 alarms of 92.5% to 95% (Paky et al Acta Paediatr. 1995 Jun; 84(6):613-6.)**

Evidence for Current SpO2 Ranges

- **No current prospective studies have evaluated actual durations of time at various SpO2 levels**
- **Median SpO2 in healthy preterm infants in room air = 97% (Ng et al Arch Dis Child 1998;79:F64)**
- **All published studies reported target ranges ie lower vs higher High SpO2 alarm limits –(92% vs 95%) for populations but did not present any data as to how well these target were adhered to.**
- **Sun et al compared units with upper limits of >95% with those of ≤ 95% (Ped Res 2002, 51:350A)**

Evidence for Current SpO2 Ranges

- **Tin et al reported units by the limits they set without any individual patient data (Tin et al Arch Dis Child 2001;84:F106)**
- **Another survey compared SpO2 limits > 98% with ≤ 98%, and early limits – first 2 weeks- of > 92% vs < 92%**

  (Anderson Ped Res 2002;51:367A)
- **Chow et al reported on a change of practice including lowering of the SpO2 limit – They did not provide any actual SpO2 data (Chow et al, Pediatr 2003;111:339)**
- **All of these studies suggested that lower SpO2 limits were associated with less ROP.**

Evidence for Current SpO2 Ranges

- **Prior to the initiation of SUPPORT – there were no data indicating the actual percent of time ELBW infants spend at different SpO2 values or ranges**
- **The design of the trial using oximeter downloads was unique and will provide this information based on a large prospective cohort**
- **This trial was also unique in collecting this data from 2 hours of age in acutely unstable ELBW infants until they are out of oxygen for 3 days.**

Response to DSMC

Safety Issue of SpO2>95%

Concern regarding safety issue of duration of SpO2 > 95%

- ✓ **The current best evidence utilizing actual oximeter data is from Hagadorn et al (PAS 2004 Abstract: Late Breaker)**
- ✓ **Evaluated 78 ELBW infants for 70 hours per week for the first 4 weeks of life**
- ✓ **Lower and upper SpO2 limits were 83% -92% and 92%-98%**
- ✓ **Median SpO2 = 95%**
- ✓ **Medians from SUPPORT Oximeter groups – 92% and 94% overall, , and 91% vs 93% for infants only in oxygen for the entire day.**

Response to DSMC:
Safety Issue of SpO2>95%

- STOP-ROP high treatment infants spent 97% of time > 95%
- Case Western a current NRN Center – Current data from SUPPORT type ELBW infants – SpO2 > 95% for > 50% time
- SUPPORT Infants on room air – SpO2 > 95% from 46% to 69% of time

Response to DSMC:
Safety Issue of SpO2>95%

- **Additional analyses evaluated the duration of time at SpO2 values of 98%, 99% and 100% as these may represent very high PaO2 values**
- **Infants in SUPPORT in ROOM Air spend 32% - 38% at these values.**
- **Infants in SUPPORT in Oxygen spend 5%-6% at these values.**

SUPPORT Trial Results - N=111, 26,889 hours

91% - 95% Room Air 85% - 89%

	%	Cum %	%	Cum%
98%	15.49%	77.15	13.65%	81.42
99%	12.94%	90.09	10.37%	91.79
100%%	9.91%	100.00	8.21%	100.00
Total	38.3%		32.2%	

91% - 95% Oxygen 85% - 89%

98%	3.51%	96.90	2.66%	97.23
99%	1.90%	98.80	1.60%	98.83
100%	1.20%	100.00	1.17%	100.00
Total	6.6%		5.4%	

Response to DSMC: Safety Issue of SpO2>95%

- **The algorithm for conversion of displayed versus actual values results in inability to create a whole value for each displayed value.**
- **The data evaluated by the DSMC had an overestimation of durations > 95% due to rounding errors inherent in the algorithm. Thus values of 95% are considered to be > 95%**
- **This represented greater than 6% of the initial calculated durations > 95% for the 91%-95% group**

Response to DSMC: Safety Issue of SpO2>95%

- **In an effort to provide better information regarding both high and low SpO2 values and avoid the problem with the re-conversion algorithm, we asked for analyses for durations > 96% and < 84% as these are values which do not require conversion and are always unaltered.**

Response to DSMC: Safety Issue of SpO2>95%

- ✘ Any calculations which incorrectly assigned infants on room air to be analyzed as receiving Oxygen would overestimate the durations > 95%
- ✘ Our data forms only reported 3 FiO2 data points daily for the first 14 days and then only a single daily value thereafter.
- ✘ Thus we were using oximeter data and assigning it based on these data points to determine the true days in oxygen
- ✓ Reanalysis based on assigning the infant to oxygen only if all 3 points for the day had an FiO2 > .21 showed markedly lower durations of SpO2 > 95% and greater than 96%

Response to DSMC: Safety Issue of SpO2>95%

Percent of time of spent at SpO2 < 84% and > 96%

RTI Analyses In Oxygen
Dec 2, 2005, N = 166, 102, 673 hrs

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.30%	14.05%
> 96%	21.45%	15.47%

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **Further analyses including only infants on Oxygen at all 3 data points for a given day**

RTI Analyses In Oxygen all 3 Points,

Dec 5, 2005, N = 127, 16,216 hrs

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	6.40%	13.3%
> 96%	12.5%	9.39%

Response to DSMC: Safety Issue of SpO2>95%

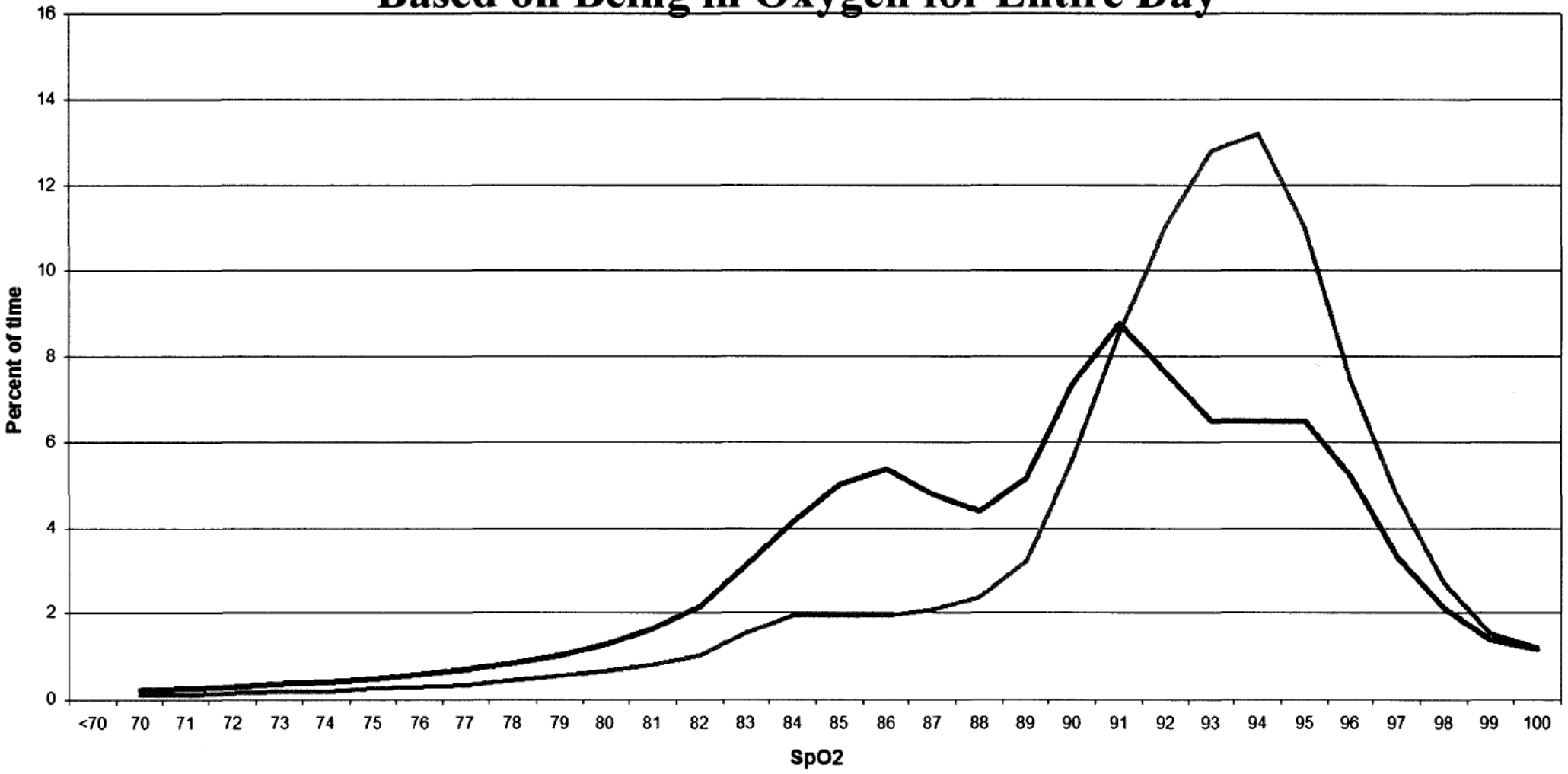
- **We believe that neither oximeter group in the SUPPORT trial is being exposed to excessive durations of SpO2 > 95% based on all currently available information and the actual SUPPORT Trial Data analyzed to date.**
- **Current analyses demonstrate that the highest duration of SpO2 > 95% was 22.9%, and > 96% was 12.5% using only infants known to be in oxygen for all 3 daily data points in the first 14 days of life.**
- **These values are previously unreported for such a population, and significantly less than the original data reviewed by the DSMC.**

Response to DSMC:

Futility regarding Separation of Oximeter Groups

- **An evaluation of the oximeter group data has revealed that there is a difference in the Mean – (90% vs 92%) and Median – (92% vs 94%) values for the 2 groups overall.**
- **The Median SpO2s obtained using only days that were in oxygen at all 3 data points were 91% vs 93%**
- **Cumulative time spent with an SpO2 of 90% or less shows an absolute difference of > 24% (22.80% -91% - 95% Group versus 47.6% -85% - 89% Group)**
- **91%-95% Group spends 77.2% of time > 90% compared with 53% for 85%-89% Group**

Percent of Time at Each SpO2 value (Smoothed data)
Based on Being in Oxygen for Entire Day



Slide 19

P9 Maybe just "Oxygen Days" ? I would make first title bigger and second smaller.
Pediatrics, 12/16/2005

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **We examined the FiO2 requirement of the infants in the Oximeter arms.**
- **If the algorithms were working as intended, then there should be a difference in the FiO2 requirement between the groups**

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **The time spent in Room Air during the first 14 days of life was 26.6% versus 35.5% for the 91%-95% group compared to the 85%-89% group.**
- **These differences persisted for data beyond 14 days**
- **The 2 groups remained separated by at least 3% duration for FiO2s of $\leq$ 50%**

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **The time in Target using only days when infants are in oxygen for all 3 data points**

91-95% = 55% 85% - 89% = 24.6%

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **The 91% - 95% Group are more in target because their alarm sounds when they reach 95%**
- ✘ **For the 85% - 89% real SpO2 values > 89% to < 92% do NOT alarm. The alarm only sounds at a reading of 95%**
- ✓ **We believe that we can improve this time in range by lowering the high alarm to 94%**

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **It is uncertain what duration of differences in either SpO2 or FiO2 will be associated with different short and long term outcomes, but we are achieving some separation in both to the present.**
- **We believe that greater separation is possible and desirable and have made a number of recommendations to ensure that this will occur.**

Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups

1. **Set high SpO2 limit – alarm to 94%. This will reduce the duration of SpO2 values > 95% for both groups, and should increase the time both groups spend in the narrow target range.**
2. **Require documentation that the oximeters alarm limits are set and functional as per protocol every 4-6 hours**
3. **Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect saturations measured while on oxygen therapy and exclude saturations of infants in room air**

Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups

4. Further training and in-service at all the sites to stress the importance of keeping the SpO2 alarms functional and at the limits of 85% and 94%. We will use the OWL (Oxygen with Love Program) developed at Oschner.
5. Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation
6. Place bedside cards to indicate the desired target range

Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups

7. Initiate compliance monitoring visits coordinated by RTI to visit random sites
8. Reanalyze group differences after an additional 100-150 infants have been enrolled.
9. Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.

Response to DSMC

- **The SUPPORT Trial Committee and the Network Steering Committee appreciate the diligence and suggestions of the Data Safety Monitoring Committee**
- **We trust that our response and suggestions to improve the SUPPORT Trial are found acceptable and that we may be allowed to continue this important trial.**

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; barbara_stoll@oz.ped.emory.edu
Subject: RE: SUPPORT ANCILLARY -Emory
Date: Monday, December 19, 2005 11:11:52 AM

Hi Barbara and Rose

If this study is intended as SUPPORT Secondary then the protocol should follow the SUPPORT Criteria ie infants of 24 0/7ths to 27 6/7ths and not include 28 week infants.

Barbara, do both of your sites enroll in SUPPORT?

I assume that the non intubated CPAP infants would not have a tracheal aspirate specimen sent.

Will this then qualify as a Secondary for the SUPPORT Trial as there will be fewer specimens from the CPAP group? (This is an assumption on my part)

However there is no intervention apart from obtaining a tracheal aspirate, and including infants in SUPPORT is not a problem as I read this protocol.

I believe that this study can move ahead.

I can send to the committee, but unless I have misread the protocol there is no interference with SUPPORT.

Let me know if either of you feels that this should be circulated.

Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, December 19, 2005 6:33 AM
To: nfiner@ucsd.edu
Subject: FW: SUPPORT ANCILLARY -Emory

Neil

Would you like me to send this to the entire subcommittee? Also, there is no budget, which I will request.

Thanks

Rose

From: Barbara Stoll [mailto:barbara.stoll@oz.ped.emory.edu]
Sent: Friday, December 16, 2005 4:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT ANCILLARY -Emory

Pkease send the attached to the SUPPORT Subcommittee-- Perhaps need to wait until restarted-- but can share with Neil FIner
BJS

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
Medical Director, Children's Healthcare of Atlanta at Egleston
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

----- Original Message -----

Friday, December 16, 2005 12:09:56 PM
Urgent Message
From: Theresa Gauthier
Subject: SUPPORT ANCILLARY ? FINAL DRAFT
To: Barbara Stoll
Susie Buchter
Anthony Piazza
LouAnn Brown
Attachments: final Protocol outline NICH.doc 152K

I have attached the ? Final outline for the proposed ancillary study to evaluate the tracheal aspirates, alveolar macrophage from the babies enrolled in SUPPORT trial- Anthony, I apologize for not including you in the earlier email about this proposal- Please review . Barbara- please get this to them before their January meeting.

Thanks everybody

TG

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Support
Date: Friday, December 16, 2005 6:27:30 PM

Let's discuss on monday...I want to understand his concern totally
---
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Spong, Catherine (NIH/NICHD) [E] <spongc@dir49.nichd.nih.gov>
Sent: Fri Dec 16 17:46:35 2005
Subject: Fw: Support

I will suggest (b) (5)
Let me know if I should respond differently??

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Alan Jobe <Alan.Jobe@cchmc.org>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Fri Dec 16 17:35:40 2005
Subject: Re: Support

OK - but I am not sure that is reasonable - a way to go around the DSMC? Through Dr. Alexander? Should I call Spong? Should I raise a fuss or just let it lie. The DSMC thing is broken at NICHD (should not have stopped the antenatal steroid trial) - can I use this to start to get it fixed - a parting shot?
--
Alan H Jobe MD Phd
Prof of Pediatrics/Neonatology
Cincinnati Childrens Hospital
3333 Burnet Ave, Cincinnati OH, 45229
Ph - 5136368563
Fax - 5136368691
Alan.jobe@cchmc.org

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Support
Date: Friday, December 16, 2005 4:59:33 PM

Monday is fine

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Spong, Catherine (NIH/NICHD) [E] <spongc@dir49.nichd.nih.gov>
Sent: Fri Dec 16 16:53:32 2005
Subject: Fw: Support

FYI
Should I update duane?? Perhaps monday? The meeting is now firm for 1/24

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: 'Alan.Jobe@cchmc.org' <Alan.Jobe@cchmc.org>
Sent: Fri Dec 16 16:47:18 2005
Subject: Re: Support

Alan
Unfortunately there was a lot of material provided and Dr. AVery requested a face-to-face meeting. This is the earliest possibility for the group to meet in person.
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Alan Jobe <Alan.Jobe@cchmc.org>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Fri Dec 16 16:29:26 2005
Subject: Support

Rose - Neil is questioning if there is a way to move the DSMC along - via Dr alexander, or whatever. I happen to agree that stopping in the first place was a bad idea, and the response is compelling - to me.

Your thoughts - on a Friday afternoon?
--
Alan H Jobe MD Phd
Prof of Pediatrics/Neonatology
Cincinnati Childrens Hospital
3333 Burnet Ave, Cincinnati OH, 45229
Ph - 5136368563
Fax - 5136368691
Alan.jobe@cchmc.org

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Subject: SUPPORT ANCILLARY -Emory
Date: Friday, December 16, 2005 4:11:23 PM
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Pkease send the attached to the SUPPORT Subcommittee-- Perhaps need to wait until restarted-- but can share with Neil FIner
BJS

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Medical Director, Children's Healthcare of Atlanta at Egleston
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Thanks everybody

TG

The effects of oxidative stress on the neonatal alveolar macrophage- an ancillary study

Theresa W. Gauthier, MD
Lou Ann S. Brown, PhD
Susie Buchter, MD
Anthony J. Piazza, MD
Barbara Stoll, MD

Department of Pediatrics
Division of Neonatology
Emory University
Atlanta, GA

December 16, 2005

A. Abstract

Premature newborns are at increased risk of pulmonary infection due to the immaturity of inflammatory cells, including the resident alveolar macrophage. The macrophage is the first line of defense against infection in the lung. Glutathione, (**GSH**) a major antioxidant in the lung, is required by the macrophage to maintain redox potential and optimize intracellular functioning. Levels of systemic and alveolar GSH are deficient in the premature newborn, placing the lung at increased risk for oxidant injury and cellular dysfunction. We ***postulate*** that the pulmonary GSH deficiency caused by prematurity is exacerbated when superimposed on exaggerated oxidant stress, such as that caused premature delivery, oxygen therapy and mechanical ventilation. We ***further postulate*** that increased oxidant stress for the resident macrophage contributes to impaired macrophage maturation and function in the premature newborn.

Studies of chronic oxidative stress from adult and fetal animal models from our laboratory have demonstrated that alveolar macrophage dysfunction contributed to a decreased clearance of bacteria from the lung, increasing bacterial sepsis and pneumonia *in vivo*. *In vitro* analysis of premature alveolar macrophage phagocytosis was improved with exogenous GSH, while apoptosis and malonyldialdehyde, a marker of severe oxidant stress were decreased with exogenous GSH. Furthermore, alveolar macrophage function correlated with the maturity of the cell. In preliminary clinical studies from premature intubated babies (n=12, birth weight ~759gms, gestational age ~26 wks), tracheal aspirate GSH was inversely related to hydrogen peroxide (H_2O_2) content, suggesting that as the oxidative stress in the airway increased, the availability of GSH decreased. Furthermore, Fas ligand, a strong apoptotic signal for cells positively correlated with H_2O_2 and negatively correlated with GSH. The ***in vitro*** phagocytic function of isolated alveolar macrophage from these premature newborns was significantly increased and apoptosis was significantly decreased by exogenous GSH. **We hypothesize that the oxidative stress of prematurity jeopardizes macrophage GSH, and resulting in increased macrophage oxidant stress, dysfunction and impaired maturation. Furthermore, we hypothesize that increased markers of oxidant stress in the tracheal aspirate correlate with delayed alveolar macrophage maturation and dysfunction.**

B. Statement of the Problem: Premature newborns are at increased risk of oxidant stress and pulmonary infection. Glutathione, (**GSH**) a major antioxidant in the lung, is required by immune cells such as the resident alveolar macrophage to maintain redox potential and optimize intracellular functioning. Levels of systemic and alveolar GSH are deficient in the premature newborn, placing the lung at increased risk for oxidant injury, macrophage dysfunction and risk of infection. The ability to identify the premature patient at risk for increased oxidant stress and alveolar macrophage dysfunction is clinically lacking. Furthermore, a better understanding of the role of the maturation of the alveolar macrophage in immune defense in the premature lung is necessary for the optimal care of these patients.

C. Hypothesis: We ***hypothesize*** that the oxidative stress of prematurity jeopardizes macrophage GSH, and resulting in increased macrophage oxidant stress, dysfunction and impaired maturation. Furthermore, we ***hypothesize*** that increased markers of oxidant stress in the tracheal aspirate correlate with delayed alveolar macrophage maturation and dysfunction.

D. Specific Aims

Aim 1- To determine whether oxidative stress markers on the alveolar macrophage of premature newborns correlate with alveolar macrophage maturity and apoptosis.
Aim 2- To determine whether neonatal alveolar macrophage maturity correlates with ***in vitro*** function and viability.

E. Rationale/justification

The premature lung is under enhanced oxidative stress. Glutathione (**GSH**)(g-glutamyl-cysteinylglycine) is an essential antioxidant in the body. GSH is normally present in high concentrations in the epithelial lining fluid (**ELF**) of the lung through active transport from the plasma to the alveolar space. In the premature newborn, plasma GSH is decreased; therefore, the alveolar GSH concentration is subsequently decreased, increasing the risk of oxidative stress in the premature lung (1-3). Indeed, GSH levels in the broncho-alveolar lavage of premature infants are inversely related to the development of CLD (2, 4). Therefore, the premature lung is a "low GSH environment" at risk for oxidant-induced injury. Furthermore, common clinical conditions have been associated with increased oxidant stress including include maternal diabetes, maternal smoking, pregnancy-induced hypertension, intrauterine growth retardation, and preterm premature rupture of membranes (5-9). **Therefore, the premature newborn is at risk of exaggerated oxidant stress.**

Understanding the functions of the neonatal alveolar macrophage is important. As the resident inflammatory cell in the lung, the alveolar macrophage provides the initial defenses for the lung against foreign and infectious particles. A professional phagocytes, the alveolar macrophage defends the lung by initiating and regulating the inflammatory process and has the responsibility to phagocytose and clear infectious particles. The majority of alveolar macrophages are derived from peripheral circulating blood monocytes. The monocyte precursors within the systemic circulation constitutively move into the interstitial space of the lung and differentiate into mature alveolar macrophage in the alveolar space. Alveolar macrophage precursors are also recruited to the lung in response to pro-inflammatory stimuli. Therefore, the normal population of alveolar macrophage is a heterogeneous mix of immature and mature cells in the human, (10). These populations of cells demonstrate functional variability in their ability to ingest organisms and release cytokines in response to infectious stimuli. The alveolar macrophage's response to inflammation, the clearance of infection and the termination of the inflammatory response all contribute to the inflammatory state of the lung. With inflammatory states, chronic disease, infection and adult respiratory distress syndrome, the heterogeneity of the alveolar macrophage population is altered to a more immature, monocytic phenotype, and these changes in macrophage population and function contribute to the severity of the local disease state in the lung (11-14). **Therefore, a better understanding of the maturation of the alveolar macrophage population in the developing lung would advance the care of the premature newborn.**

Glutathione is necessary for alveolar macrophage functioning. In the newborn infant, particularly the premature newborn, the function of the alveolar macrophage is also impaired (15, 16). Within the lung, GSH is an essential substance for the resident cells of the airway, including the alveolar macrophage. The alveolar macrophage is dependent on the availability of extracellular GSH to maintain intracellular concentrations of GSH during hyperoxia (17). The intracellular antioxidant defenses of the macrophage and its phagocytotic ability are dependent on a functional intracellular GSH redox system (18, 19). With exaggerated intracellular oxidative stress, the increased production of reactive oxygen species within the macrophage exceeded the cell's ability to detoxify them, contributes to its own demise via programmed cell death or apoptosis (20). **Therefore, increased oxidant stress in the lung causes dysfunction and apoptosis of the alveolar macrophage, decreasing the lung's defenses against bacterial infection.**

Chronic oxidative stress increases the risk of infection in several disease states. The chronic depletion of antioxidants such as GSH has been well described in other pediatric conditions such as

cystic fibrosis. With chronic GSH depletion, the inability to increase epithelial lining fluid GSH in response to infection contributes to the increased risk of pulmonary infections characteristic of cystic fibrosis (21, 22). Chronic oxidative stress and decreased GSH availability also contributes to alveolar macrophage dysfunction and the increased risk of infection and acute lung injury in adults alcoholics (23-28). Premature newborns are well known to be at an increased risk of infections (29-32), increasing morbidity and adverse outcomes for the premature newborn (33, 34). **However, the relationship between oxidant stress, alveolar macrophage maturation and infection risk in the premature remains under investigation.**

F. Background / Previous Studies

1. Chronic oxidant stress impairs alveolar macrophage clearance of bacteria *in vivo*. Recent studies in our laboratory have investigated the effects of chronic oxidative stress on alveolar macrophage function in the adult rat and the newborn guinea pig. Using chronic ethanol (E) exposure as a model of chronic oxidant stress and diminished GSH availability in the adult lung (28), we examined the clearance of bacteria from the lung *in vivo*. In preliminary experiments, bacterial clearance of *group B strep* (GBS) was dramatically diminished with E exposure. Systemic blood culture demonstrated an over 200 fold increase in growth in the E animal compared to control (Control 22 ± 10 vs E 4,866 ± 1,737 colony forming units (CFU), p=0.1). Furthermore, E exposure significantly decreased bacterial clearance in lung homogenates (Control-67 ± 35 CFU vs. E-1400 ± 305 CFU $p<0.05$). In a guinea pig model of *in utero* oxidant stress and diminished GSH availability due to fetal E exposure (35), term guinea pigs were evaluated for clearance of experimental GBS. Bacterial clearance was dramatically diminished in the blood (Control 41.3 ± 41 CFU vs E-12,500 ± 2,500 CFU) and in the lungs (Control 0.50 ± 0.58 vs E- 90.5 ± 3.5 CFU)of E exposed pups compared to control. Furthermore, alveolar macrophage phagocytosis of the GBS was diminished in E exposed pups compared to control (Control- 96.3 ± 3.7% positive vs E- 56.8 ± 13.5% positive). **Therefore, chronic oxidant stress of ethanol exposure diminished alveolar macrophage phagocytosis of experimental GBS, decreasing bacterial clearance in the lung and increasing sepsis in these animal models.**

2. GSH improves fetal alveolar macrophage phagocytosis and viability *in vitro*. Our laboratory has evaluated premature alveolar macrophage function using the timed-pregnant guinea pig (term 72 days) (35). Alveolar macrophage were isolated from 55 day pups by bronco-alveolar lavage and incubated with FITC-labeled inactivated staph aureus for 4 hrs. *In vitro* analysis has demonstrated that exogenous GSH (200 μM *in vitro*) significantly improved the phagocytic index (PI= relative fluorescent units of FITC-labeled staph aureus/cell x % of cells positive for any fluorescence) of the premature alveolar macrophage (- GSH 1742.57 ± 90.54 vs. + GSH 2243.51 ± 154.19, $p<0.05$). Additional experiments have demonstrated that the maturity of the alveolar macrophage, as determined by a guinea pig marker, significantly correlated with the function of phagocytosis (Spearman Rank order 0.25, p=0.017). Apoptosis of the alveolar macrophage was also significantly diminished with exogenous GSH *in vitro* (–GSH 22.92 ± 3% of the cells vs. + GSH 15.8 ± 1.1%, $p<0.05$). Finally, malonyldialdehyde, a lipid peroxidation product and a marker of severe oxidant stress on the alveolar macrophage was also significantly reduced with the addition of GSH *in vitro* (– GSH 31.6 ± 2.8% of cells positive by immunofluorescence vs + GSH 23.9 ± 2.7 %, $p<0.05$). **These results suggested that exogenous GSH improved function and viability of the premature alveolar macrophage, decreasing oxidant stress.**

3. Oxidant stress is present in the airway of premature newborns. We isolated and examined tracheal aspirate fluid (**TA**) and macrophage from intubated premature newborns within 24 hr of

intubation. Twelve patients with birth weight 759 ± 80 gm and gestational age 25.7 ± 0.1wk were evaluated. The majority had hyaline membrane disease (10/12) and received surfactant therapy (10/12). The TA was evaluated for GSH and its oxidized portion GSSG via HPLC(28, 35). Hydrogen peroxide (H_2O_2) in the TA was measured via colorimetric assay. The ratio of GSH/GSSG in the TA negatively correlated with H_2O_2 (Pearson -0.829, $p<0.05$), suggesting that as the oxidative stress in the airway increased, the availability of GSH decreased. Because soluble Fas ligand (**FasL**) has been associated with an acute inflammatory state and is a strong apoptotic signal for cells such as neutrophils and type II epithelial cells, (36, 37)(23, 27) we measured FasL in the TA. H_2O_2 positively correlated with FasL (Pearson: +0.916, $p<0.01$), while GSH/GSSG negatively correlated with FasL (Pearson: -0.991, $p<0.01$). **These results support the hypothesis the imbalance of oxidative stress and decreased GSH/GSSG may contribute to increased signals for cellular oxidative stress and apoptosis in the premature airway.**

4. Function and viability of premature newborn alveolar macrophage was improved with exogenous GSH *in vitro*. The premature alveolar macrophage were evaluated *in vitro* for phagocytosis and apoptosis. The addition of GSH (200 μM for 4h *in vitro*) nearly doubled the phagocytic index of the cells (PI without GSH- 2368 ± 321 vs PI with GSH 4062 ± 389). Although the cells were uniformly viable at the time of isolation as measured by the calcein/ethidium iodine Alive-dead stain,@ the addition of GSH (200 μM) *in vitro* dramatically reduced macrophage apoptosis by ~70% (52.6 ± 4% vs 15.7 ± 1%, $p<0.01$). **Therefore, these data suggest that the addition of GSH to the culture media improved function and viability of premature alveolar macrophage.**

G. Method/ Procedures

*1. **Description of study design:*** This proposal would be an Ancillary study to the current SUPPORT trial. Since the analyses focus on the relationship between oxidant stress markers and alveolar macrophage maturation, each baby's sample would be compared to itself. With the exception of sample collection, there is no intervention to the patient.

2. Definition of study population (with inclusion/exclusion criteria)

Patient Population: Tracheal aspirate samples will be obtained for alveolar macrophage analysis from participating NICHD NICUs. Locally at the Emory University NICUs, tracheal aspirate samples will be obtained for alveolar macrophage analysis and fluid analysis from two hospitals (Crawford Long Hospital and Grady Hospital) within the Emory University Division of Neonatology system.

Patient Enrollment: After admission to the neonatal intensive care unit, patients will be evaluated for enrollment in the study.

Inclusion criteria: All newborns admitted to the NICU with gestational age of 24-28 weeks who require endotracheal intubation will be eligible for enrollment.

Exclusion criteria: Patients with suspected chromosomal abnormality, positive maternal HIV, or refusal of consent are excluded. Patients deemed non-viable by the attending neonatologist will not be approached for enrollment. An HIV history will be exclusion because of the potential risk to laboratory personnel in the sample handling and subsequent fluid and macrophage analysis.

3. Description of study intervention

Tracheal Aspirate Sample collection: After verbal informed consent (Emory Univ IRB, Gauthier #388.99), the TA will be obtained at the time of routine endotracheal suctioning at <24 hrs after intubation, daily for 3 days, day 7 and then weekly until the baby is no longer on the ventilator. For the suctioning procedure, bacteriostatic saline (~1 cc) is instilled into the trachea and after several ventilator breaths the sample is retrieved into a closed, sterile (Leukins) trap. The sample will be obtained after suctioning is performed for clinical indications. Patients and samples will be identified with a study number to ensure confidentiality. The PI will match study numbers to medical record numbers, with confidentiality maintained. Universal sterile technique will be used for all sample handling and processing. For samples obtained from distant NICHD NICU's, the sample will be immediately transferred into a labeled test tube containing fixative media and labeled with the study number. These sampled would be shipped to the Neonatology Laboratory of Emory University, Atlanta, GA. For samples collected locally in Atlanta, the labeled sample will immediately be placed on ice and transported to the Neonatology laboratory. Sample collection is straightforward and easy, requiring minimal time and preparation.

4. Precise definition of primary/secondary outcomes

Primary Outcome (all samples)- The correlation between alveolar macrophage oxidant stress and the alveolar macrophage's maturational profile.

1. Macrophage oxidant stress- Fixed alveolar macrophage will be recovered from the TA and evaluated under fluorescent immunohistochemistry for markers of oxidant stress including malonyldialdehyde (MDA) and hydroxynonenal (HNE) (35).
2. Macrophage maturational profile will be evaluated by fluorescent confocal microscopy as outlined in **Table 1** below. Macrophage apoptosis will be measured by fluorescent cleavage of poly (ADP-ribose) polymerase (PARP), an early indicator of the apoptosis pathway (38).

Table 1 Evaluation of alveolar macrophage maturational profile

Cell Characteristic	*Mature*	*Immature*
Size	Large	Small
Nuclear/Cytoplasmic Ratio	Low	High
Markers	CD 14 low/CD11b low/CD32 high, Mannose Receptor high/ FCγRIII high	CD 14 high/ CD11b high/CD32 low/Mannose Receptor low/ FcγRIII low
Apoptosis	Decreased	Increased

Secondary Outcomes (to be evaluated on local samples in Atlanta):

1. The correlation between alveolar macrophage phagocytic function and maturational profile as described above. *In vitro* analysis of alveolar macrophage phagocytic function will be examined using inactivated FITC-labeled staph aureus.

2. The correlation between TA oxidative stress (GSH/GSSG, H_2O_2) and alveolar macrophage maturational profile and cell oxidative stress will be evaluated as described above. TA GSH/GSSG will be measured via HPLC while H_2O_2 will be measured via colorometric assay. Cellular protein-bound GSH status will be also evaluated on fresh alveolar macrophage using a primary antibody to GSH.

5. Sample size estimate with some statistical support (including estimate of compliance and consent rates) based upon primary outcome.

In order to detect the strength of a correlation between macrophage oxidant stress markers and maturational profile, and function and maturational profile, we will assume that the data is not normally distributed and the variables are neither dependant nor independent of each other. Using Sigma Stat for Windows and the Spearman Rank Order Correlation, we will calculate the Spearman correlation coefficient **rs**. Assuming a negative correlation coefficient of -0.4 (as oxidant stress increases, maturation decreases) or positive +0.4 (as maturation increases, function increases) we will need a sample size of 47 patients with an alpha of 0.05 and a 0.8 power. Our current consent rate at the Emory University hospitals is ~67% of eligible infants.

6. Available population/compatibility with other ongoing protocols. Locally at the Emory University NICUs, tracheal aspirate samples will be obtained for alveolar macrophage analysis and fluid analysis from two hospitals (Crawford Long Hospital and Grady Hospital) within the Emory University Division of Neonatology system. Both hospitals have active delivery services in the city of Atlanta. Crawford Long Hospital delivers ~ 3,600 deliveries/year, serving both suburban and urban patients. Crawford Long Hospital has a new 25 bed Level III Neonatal Intensive Care nursery. Grady Hospital serves predominantly the urban community with ~4,000 deliveries/year and is equipped with a ~60 bed Level III Neonatal Special Care nursery. From Grady hospital and Crawford long hospital infants <1500 g and requiring intubation totaled 126 infants in 2003. This proposed analysis of alveolar macrophage should not interfere with other ongoing trials. Study medications or other interventions (if applicable) will be noted during the macrophage analysis.

7. Estimate of projected recruitment time

We estimate that 1 year will be needed to recruit and obtain enough clinical samples to obtain statistical significance in the macrophage analysis as described above. Enrollment from the entire network would increase enrollment from approximately 10 patients per month to approximately 30 patients per month.

H, Risks/benefits, with estimate of frequency/severity of risks.

The intervention of tracheal suctioning is not without risks of infection/damage to the airway. However, we propose to evaluate cells and tracheal aspirate fluid obtained from routine tracheal suctioning, when used only for clinical indications, as per individual NICU routine. Therefore, there are no other risks to the patient from this proposal. There are no direct benefits for the individual subjects to participate in this proposal.

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From:	Neil Finer
To:	"Das, Abhik"; Higgins, Rosemary (NIH/NICHD) [E]
Cc:	"Avroy A. Fanaroff, M.D."; "Hastings, Betty J."; "Ed Donovan"; "Poole, W. Kenneth"; "Maynard Rasmussen"; "Michele"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Subject:	RE: OWL
Date:	Friday, December 16, 2005 9:47:01 AM

Thanks Abhik
I have already mentioned OWL in the presentation and will add one or 2 more slides about it.
Neil

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, December 16, 2005 6:40 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Cc: Avroy A. Fanaroff, M.D.; Hastings, Betty J.; Ed Donovan; Poole, W. Kenneth; Maynard Rasmussen; Michele; Shahnaz Duara; Wade Rich; Wally Carlo
Subject: RE: OWL

Yes; I think this is a very good idea and would show the DSMC our seriousness with respect to the separation issue. I would suggest just weaving it into Neil's presentation as part of the steps we would take to address the separation issue (maximum 2 slides), and give more details only if asked for (would keep them handy though, just in case).

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 16, 2005 9:35 AM
To: nfiner@ucsd.edu
Cc: Avroy A. Fanaroff, M.D.; Hastings, Betty J.; Das, Abhik; Ed Donovan; Poole, W. Kenneth; Maynard Rasmussen; Michele; Shahnaz Duara; Wade Rich; Wally Carlo
Subject: RE: OWL

HI,
This information is helpful - one word of caution though. I think we have given the DSMC a fair bit of material thus far. Perhaps the summary document is appropriate, but I am concerned that the entire package may be a bit too much. Others thought would be appreciated, especially Ken and Abhik.

Thanks
Rose

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, December 15, 2005 5:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; Das, Abhik; 'Ed Donovan'; 'Ken Poole'; 'Maynard Rasmussen'; 'Michele'; 'Neil Finer';

'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
Subject: FW: OWL

Hello Rose and Everyone
I would like you to look at this information. I believe that we could use this as we plan to move ahead with SUPPORT to encourage better attention to oximeter alarms. Would you let me know if you think that some or all of these materials would be useful for SUPPORT?
I have asked for permission to use in the Network and Jay Goldsmith has already said yes.
The tentative DSMC meeting looks like Jan 24th in DC.
Thanks
Neil

-----Original Message-----
From: Margaret Thibodeaux [mailto:mthibodeaux@ochsner.org]
Sent: Thursday, December 15, 2005 7:24 AM
To: nfiner@ucsd.edu
Subject: OWL

Enclosed is the information that you requested from Dr. Goldsmith. Attached are the documents we used to get started. There is the Potentially Better Practice Sheet, The contract we had each employee sign, a copy of the Logo, the worksheet for data collection, a copy of the bedside summary, (was laminated and placed at each OWL's bedside), and the form used to do the q shift walk throughs for compliance.

We did not have any special materials for the family. There was a copy of the protocol guidelines attached to each OWL's bedside, and for those who asked, an explanation of the protocol was given.
We did not get any negative feedback from the staff in relation to the families, just a sense of a greater need of awareness for the nurses and therapists at the bedside.
When we initiated the protocol all babies under 1500 gms were but on the protocol, even those that had been with us prior to the date of initiation.
We did not experience any complaints or major problems with the implementation or the families awareness of it.
I also attached a power point presentation that we used to initiate the education to the unit.We started with the Neo Docs and had them all agree that this would be a change of policy and unit protocol to be followed by all unless an order was written with a substantiated reason for not following the protocol.
The frequent alarms and frequent changes in the o2 sats and requirements are part of the deal. We found there is a period of time that all of the micro premies experience this and it stops with time. It can be very challenging for the bedside nurse. You may find the contract helpful. We also found the nurses took personal responsibility for making sure their primary did not need cryo.
We also have a large amount of very senior staff. We did have small amount of trouble with compliance in the beginning.
We did a large amount of education prior to initiating the change. We published (in the unit) our numbers compared to the national average, (our numbers were much worse). I kept the staff updated with current data, what their compliance was as well as our ongoing ROP numbers.

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; "Stevens, Timothy"
Cc: "Phelps, Dale"
Subject: RE: Breathing Outcomes Study
Date: Friday, December 16, 2005 9:31:28 AM

These changes look fine to me
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 16, 2005 4:44 AM
To: Stevens, Timothy; Neil Finer
Cc: Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Breathing Outcomes Study

Hi
I have made a few suggested editorial changes - let me know if thesea
rea ok with you and we can proceed at the sites.

THanks
Rose

From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Thu 12/15/2005 5:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Neil Finer'
Cc: Phelps, Dale
Subject: RE: Breathing Outcomes Study

Hi Neil and Rose,

Attached is a draft of a proposed letter for study coordinators to
submit to
their IRB, encouraging them to actively consider the Breathing Outcomes
Study as a secondary to SUPPORT. For reference, I attached the sample
consent from the Breathing Outcomes manual for patients already enrolled
in
SUPPORT.

Thanks

Tim

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, December 15, 2005 4:23 PM
To: Stevens, Timothy; Neil Finer
Cc: Phelps, Dale
Subject: RE: Breathing Outcomes Study

Tim

Please compose a letter and send it to Neil and I and we can send out to

the network

Thanks
Rose

-----Original Message-----
From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Thursday, December 15, 2005 4:19 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Neil Finer'
Subject: Breathing Outcomes Study

Hi Neil and Rose,

With the main SUPPORT Trial on hold, many coordinators have not taken the
Breathing Outcomes Study to their IRBs and some IRBs have been reluctant

to
consider an amendment allowing the Breathing Study to go forward.

With your consent, I'll prepare a cover letter and consent form for the coordinators to present to their IRB explaining that the Breathing Outcome
Study population is infants already enrolled in SUPPORT and that, while the
main trial is on hold, the follow up windows (timepoints) are passing and
cannot be recouped. The letter will request IRB review so that patients currently enrolled in SUPPORT may be approached for consent, using a consent
form separate from the SUPPORT consent, authorizing enrollment into the Breathing Outcome Study. The letter will emphasize that no new recruitment
into SUPPORT will occur until the study officially resumes.

If this is OK with you, I'll get it out this week.

Thanks

Tim

From: Neil Finer
To: "Stevens, Timothy"; Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Phelps, Dale"
Subject: RE: Breathing Outcomes Study
Date: Thursday, December 15, 2005 5:48:26 PM

This looks fine to me
Neil

-----Original Message-----
From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Thursday, December 15, 2005 2:46 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Neil Finer'
Cc: Phelps, Dale
Subject: RE: Breathing Outcomes Study

Hi Neil and Rose,

Attached is a draft of a proposed letter for study coordinators to submit to their IRB, encouraging them to actively consider the Breathing Outcomes Study as a secondary to SUPPORT. For reference, I attached the sample consent from the Breathing Outcomes manual for patients already enrolled in SUPPORT.

Thanks

Tim

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, December 15, 2005 4:23 PM
To: Stevens, Timothy; Neil Finer
Cc: Phelps, Dale
Subject: RE: Breathing Outcomes Study

Tim
Please compose a letter and send it to Neil and I and we can send out to the network

Thanks
Rose

-----Original Message-----
From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Thursday, December 15, 2005 4:19 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Neil Finer'
Subject: Breathing Outcomes Study

Hi Neil and Rose,

With the main SUPPORT Trial on hold, many coordinators have not taken the
Breathing Outcomes Study to their IRBs and some IRBs have been reluctant to
consider an amendment allowing the Breathing Study to go forward.

With your consent, I'll prepare a cover letter and consent form for the coordinators to present to their IRB explaining that the Breathing Outcome
Study population is infants already enrolled in SUPPORT and that, while the
main trial is on hold, the follow up windows (timepoints) are passing and
cannot be recouped. The letter will request IRB review so that patients currently enrolled in SUPPORT may be approached for consent, using a consent
form separate from the SUPPORT consent, authorizing enrollment into the Breathing Outcome Study. The letter will emphasize that no new recruitment
into SUPPORT will occur until the study officially resumes.

If this is OK with you, I'll get it out this week.

Thanks

Tim

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD) [E]
Cc:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; Das, Abhik; "Ed Donovan"; "Ken Poole"; "Maynard Rasmussen"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Subject:	FW: OWL
Date:	Thursday, December 15, 2005 5:40:29 PM
Attachments:	OXYGEN WITH LOVEf.ppt OXYGEN WITH LOVE WORKSHEET.doc SEYMOUR.doc OXYGEN WITH LOVEcontract.doc Potentially Better Practice Concept.doc blankowl.xls OWL SUMMARY.doc owl shift.xls

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Hello Rose and Everyone
I would like you to look at this information. I believe that we could use this as we plan to move ahead with SUPPORT to encourage better attention to oximeter alarms. Would you let me know if you think that some or all of these materials would be useful for SUPPORT?
I have asked for permission to use in the Network and Jay Goldsmith has already said yes.
The tentative DSMC meeting looks like Jan 24th in DC.
Thanks
Neil

-----Original Message-----
From: Margaret Thibodeaux [mailto:mthibodeaux@ochsner.org]
Sent: Thursday, December 15, 2005 7:24 AM
To: nfiner@ucsd.edu
Subject: OWL

Enclosed is the information that you requested from Dr. Goldsmith. Attached are the documents we used to get started. There is the Potentially Better Practice Sheet, The contract we had each employee sign, a copy of the Logo, the worksheet for data collection, a copy of the bedside summary, (was laminated and placed at each OWL's bedside), and the form used to do the q shift walk throughs for compliance.

We did not have any special materials for the family. There was a copy of the protocol guidelines attached to each OWL's bedside, and for those who asked, an explanation of the protocol was given.
We did not get any negative feedback from the staff in relation to the families, just a sense of a greater need of awareness for the nurses and therapists at the bedside.
When we initiated the protocol all babies under 1500 gms were but on the protocol, even those that had been with us prior to the date of initiation.
We did not experience any complaints or major problems with the implementation or the families awareness of it.
I also attached a power point presentation that we used to initiate the education to the unit.We started with the Neo Docs and had them all agree that this would be a change of policy and unit protocol to be followed by all unless an order was written with a substantiated reason for not following the protocol.
The frequent alarms and frequent changes in the o2 sats and requirements are part of the deal. We found there is a period of time that all of the micro premies experience this and it stops with time. It can be very challenging

for the bedside nurse. You may find the contract helpful. We also found the nurses took personal responsibility for making sure their primary did not need cryo.
We also have a large amount of very senior staff. We did have small amount of trouble with compliance in the beginning.
We did a large amount of education prior to initiating the change. We published (in the unit) our numbers compared to the national average, (our numbers were much worse). I kept the staff updated with current data, what their compliance was as well as our ongoing ROP numbers.

Oxygen saturation targeting to decrease oxygen's toxic effects

– Brought to you by the Ochsner Vermont Oxford Respiratory Group

OXYGEN TARGETING

- -used to decrease the risk of ROP and the need for interventional surgery; as well as other side effects of oxygen toxicity.

This is not a study!

It is a change in the way we **Practice**

Why?

- A recent multicenter study showed that 30% of infants with ROP that reached threshold and received surgery, had unfavorable vision as long as 10 years out
- We need to not only reduce the incidence of the need for surgery but decrease the number of infants that reach threshold disease

GOALS

- Decrease the incidence of ROP
- Decrease the need for interventional surgery
- Decrease total days on the ventilator
- Decrease the total days in oxygen
- Decrease length of Hospital stay

PLAN

- All admits 500-1500gms
- Oxygen or ventilator dependent
- Pusle oximeter alarms to be set at 80-95 with the goal being to keep saturations greater than 85 but less than 93

Active participation required

- Physicians
- NNP's
- Nurses
- Respiratory Therapists

Education

- Dr. Goldsmith will meet with the NNP's, Nurses, and Respiratory therapists to educate them on the relationship between oxygen and ROP
- Flip chart
- Bedside education by the VO Respiratory group
- Introduction of the contract to the NICU employees.

Statement of Understanding and Agreement

- Each NICU staff member will be expected to sign a contract with the unit. It outlines the policy, the reason for it , and at the end, each will sign stating that they have read the information, understand it, and agree to comply with the plan.

How will we monitor our progress?

- At risk infants will be identified on admit, an order written, and their bed labeled with an OWL ICON.
- Once a shift the Charge nurse will walk through the unit at a previously undetermined time and document the actual saturation reading on each at risk infant
- If the infant is not within parameters she will document why
- The data will be collected and compliance reported to the NICU staff weekly.

Compliance?

- Saturations within the desired range-initiated in the delivery room
- Minimize abrupt Fio2 changes
- Prevent large swings in the O2 saturations
- Avoid periods of O2 saturation greater than 95%.

Goal

- Compliance at least 80% of the time.

How long do we follow them?

- Saturations will be documented each shift as long as the infant is oxygen or ventilator dependent, and weighs 500-1500 gms.
- After 1500 gms we will continue to monitor the infant for ROP, need for surgery, time on ventilator, time in oxygen, and length of stay.

After we reach 80% compliance

- We start collecting data on all of our long term goals
- Each year we will compare them to our baseline year.

Saturation Parameters will vary in other groups

- PPHN
- ECMO
- CDH
- Term infants

- The NNP's will order specific oxygen saturation parameters for each infant
- If the infant is an OWL candidate an order will be written to initiate this protocol, but remember to initiate saturation targeting at delivery if the baby is 1500gms or less.

Chow study

Results:

- Decreased ROP 3 and 4 from 12.5% (1997) to 2.5% (2001)
- Decrease need for laser surgery from 4.5% (1997) to 0 in 1999-2001.
- Compared results to Vermont Oxford Network data(430 NICU's)

- The following slide shows the studies results compared to VON data. It compares the rate of Stage 3 and 4 ROP.

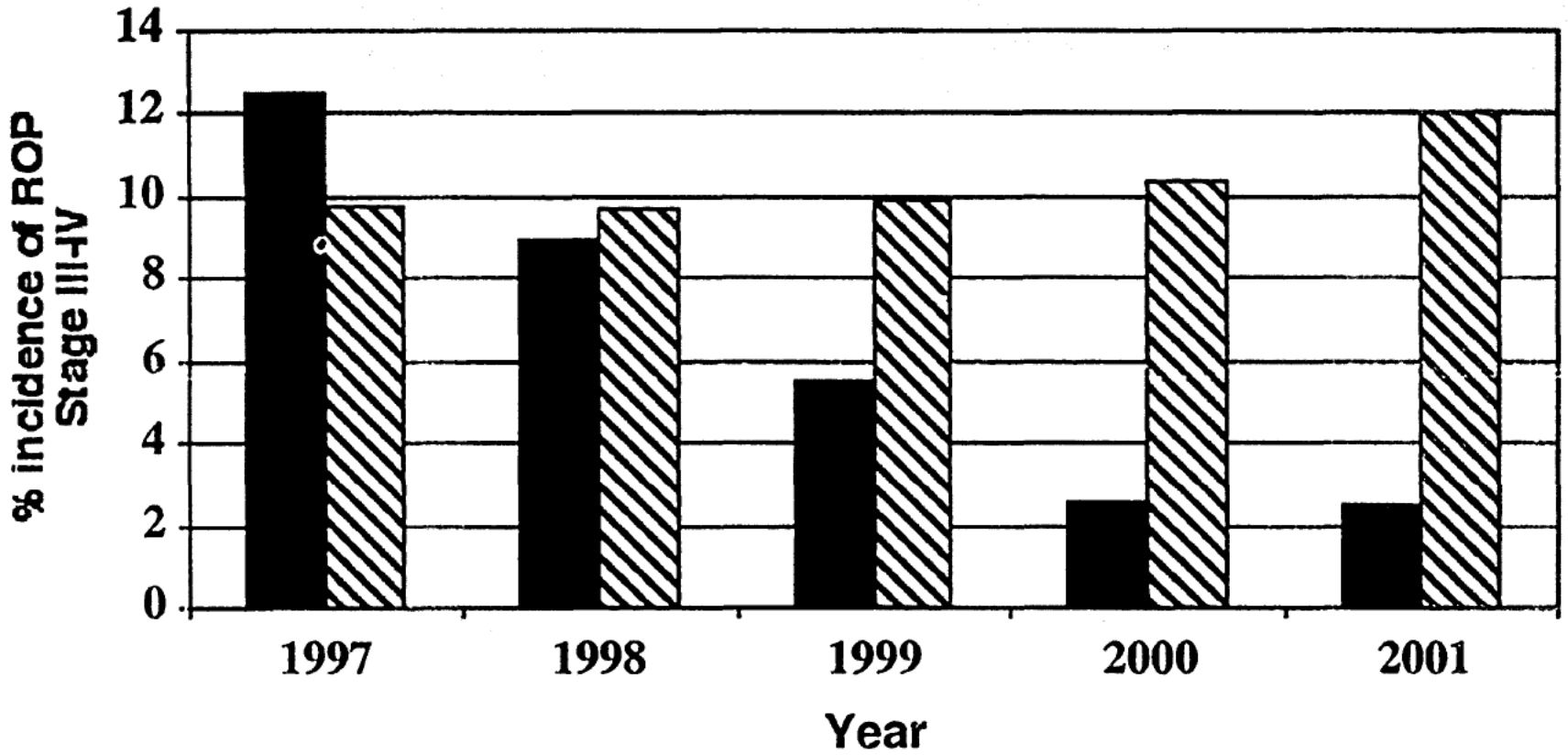


Fig 2. Incidence of ROP stages 3 to 4 for infants with birth weight of 500 to 1500 g at CSMC (■) and VON (▨) for the years 1997 to 2001. (Rates are calculated as described in "Methods.")

- The next slide shows the same comparison but of Lazer/Cryosurgery.

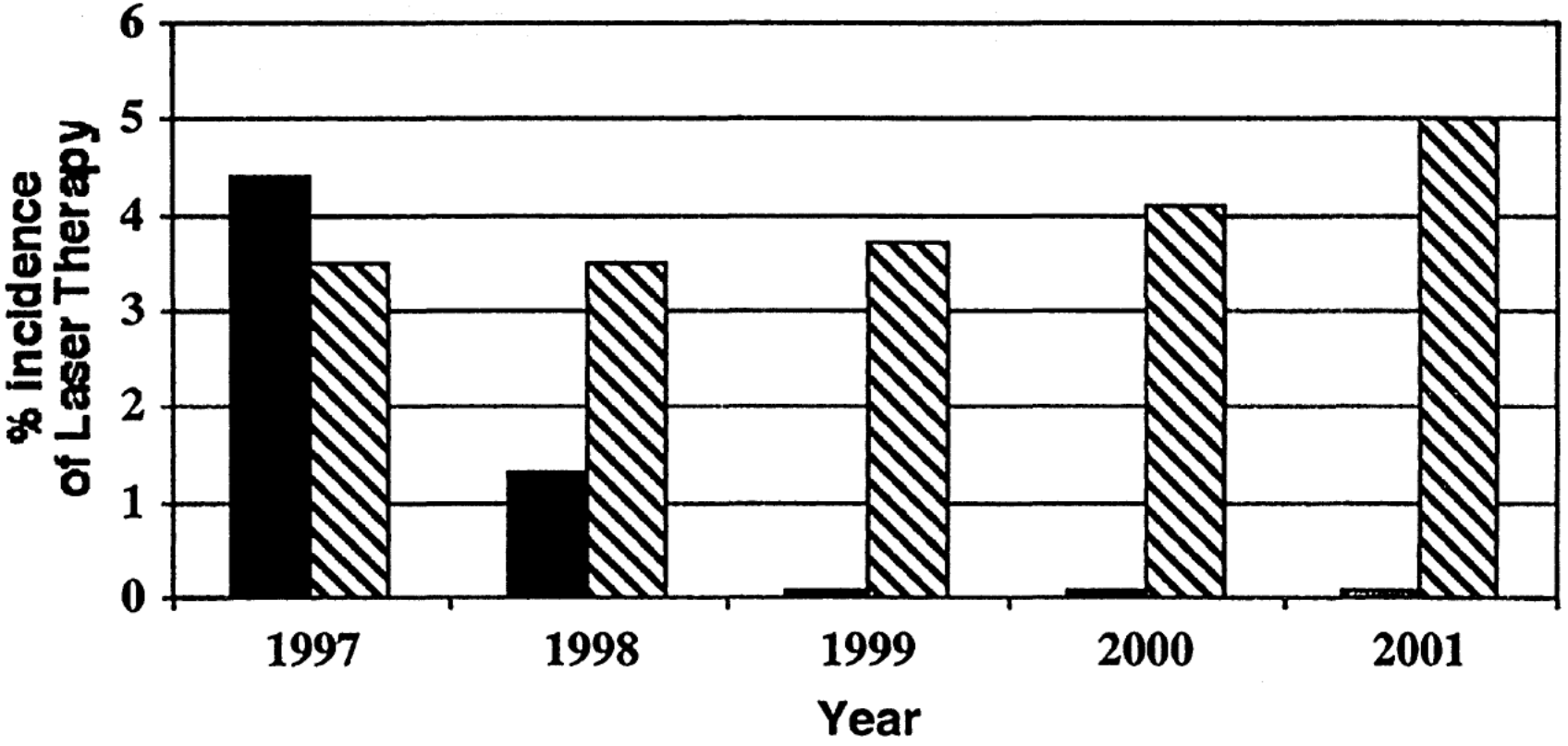


Fig 5. Incidence of ROP laser therapy for infants with birth weight of 500 to 1500 g and born at CSMC (■) and in the VON (▨) for 1997 to 2001.

What did we find at OCF?

- From 8/01 to 8/02
- 89 infants 1500gms or less
- 21 deaths/15 inborn
- 3 were short stay
- Of the remaining 65, 16 required interventional surgery (24.6%)
- 4 had stage 3 or 4 disease and did not require surgery
- 10 went home on O2(one is still here)
- 4 of those 10 required interventional surgery

OCF compared to VON

- Our ROP Lazer/Cryo surgery rate for the year 01-02 was 24.6% as compared to the national average of 5%.
- We have a lot of work to do to improve these numbers which in turn improves the eye sight of the infants that we care for.

Evidence

4 separate oxygen targeting studies have been completed to date. All 4 showed decreases in the degree of ROP as well as almost eliminating the need for interventional surgery.

What do we do?

- We can be excited about the possibility of what we can do for our patients by intervening when needed to keep their oxygen saturations at levels that minimize their risk of ROP.

The CONTRACT

- This is an explanation of what we are targeting, when to make changes and when to notify the MD/NNP of significant changes in the need for O2.
- It is an **NICU policy**.

OXYGEN WITH LOVE WORKSHEET

Name _____

Clinic Number _____

Gestational Age _____

Birth Weight _____

Birth Date _____

Admit Weight _____

Admit Age _____

Days on the ventilator _____

Days on CPAP _____

Hospital days _____

Worst ROP _____

Surgical Intervention _____

Birth Place _____

Apgars _____

Steroids _____

Comments

_____

_____

Oxygen With Love

SEYMOUR

Oxygen With Love

SEYMOUR

OXYGEN WITH LOVE

Management of Oxygen Concentrations and Oxygen Saturations in the VLBW Infant In the OCF NICU

OBJECTIVE: To avoid hyperoxia and high/low swings in oxygen saturations in the Very Low Birth Weight (VLBW) infant. (<1500g)

1. Initiate the protocol with the admission of each infant weighing 1500 gms or less.
2. No VLBW infant will be subject at any time to repeated swings in the amount of O2 being delivered in response to the saturation readings outside the acceptable range.

STATEMENTS OF PRACTICE:

a. Oxygen should be used as a drug with potentially toxic side effects. Too much can be as damaging as too little. There is no evidence that VLBW infants need saturations in the 95-100% range and these levels are potentially dangerous. It is also significant that repeatedly alternating episodes of hypoxia and hyperoxia can cause significant alterations in the vascular tone of VLBW infants

b. Saturation alarms: be sure to make the appropriate response in dealing with an alarm
- Is the pulse wave appropriate?
- Is there artifact interference?
- Assess the infant's respiratory effort and heart rate.
- How low and how long? Has the saturation been down low enough for long enough to warrant an increase in Fio2

c. Alarm settings: The alarms should be set at 80-95. They should be changed only with an order. The alarms should not be disabled at any time

d. Weaning FiO2 and oxygen saturation levels:
- Wean by 2-5% at a time if the saturation is on the high side. (>93%) Return to baseline within 10 minutes.
- Weaning should be done as fast as necessary to avoid extended periods of Hyperoxia. (But not faster than 2-5% at a time)
- Avoid weaning in increments >5% at a time; this could result in hypoxia, which would then lead to increasing the FiO2 again.

e. Increasing the FiO2:
- When an increase is needed in the FiO2, the person making the change should stay with the infant until it has reached a stable saturation level.
- An MD/NNP must be notified for any sustained need for an increase in FiO2 greater than 10% from the previously stable FiO2.

f. During and after procedures:
- FIO2 should not be routinely increased prior to a procedure. Respond appropriately to the needs of

the infant based on the saturations as well as the length and type of procedure.

- Monitor the infant after suctioning the ETT until the baby returns to a stable baseline.
- Consider that other settings (rate, PIP, CDP) may need to be changed for a prolonged procedure.

f. Spontaneous oxygen desaturations:

- The Nurse and the Respiratory therapist should work together to assess both the infant and the ventilator and/or oxygen delivery systems.
- Decide together whether an MD/NNP needs to be notified for intervention other than increased FIO2

g. Apnea:

- Choose the appropriate response based on the exam of the infant; increased respiratory rate, increase the approved parameters, use tactile stimulation, or in severe cases manual ventilation.
- If the baby does not return to the previously stable baseline (same FIO2) within 10 minutes, the MD/NNP should be notified.

SUMMARY:

BASELINE FOR THE VLBW INFANT (birth weight <1500 g)

1. Set oxygen saturation monitor alarm limits at 80-95%.
2. Do not "TITRATE" FiO2 (risky to create extreme ups and downs in the infants saturations.) Allow baby to fluctuate within the desired saturation parameters, making small movements up and down on FiO2 as needed.
3. Based on assessment wean actively by 2-5% for saturations on the high side of parameters
4. Never increase the FiO2 without first assessing the baby.

5. If the need for increased FiO2 is sustained, the MD/NNP must be notified.
6. Document saturation levels and oxygen requirements clearly (as per unit policy)
7. When altering the oxygen being delivered stay with the infant until the saturations have stabilized within an acceptable range

---

Sign below and return to PCC"S or James O'Connor

OXYGEN WITH LOVE (management of inspired oxygen concentrations and saturations in the VLBW infant)

I certify that I have read and understand the above practice plan, and I agree to follow this protocol when working with VLBW infants in the Ochsner Clinic Foundation NICU.

_____

PRINT NAME

_____

SIGNATURE

_____

DATE

Adapted form the policy prepared by Augusto Sola, MD, Published in *Pediatrics* (February 2003);111:339

Potentially Better Practice Concept: Worksheet

Topic Area: Respiratory

Potentially Better Practice: Oxygen Targeting to avoid hyperoxia in infants at risk for retinopathy of prematurity and chronic lung disease.

Rationale: Controlled reduced oxygen dosing may decrease the incidence of retinopathy of prematurity and chronic lung disease.

Classifying the strength and quality of the evidence:

1. Strong evidence from at least one systemic review of multiple well designed randomized controlled trials.
2. Evidence from a well-designed non-experimental study preferably from more than one center or research group.
3. Opinions of respected authorities, based on clinical evidence, descriptive studies or reports of expert committees.

Pertinent References:

1. The STOP-ROP Multicenter Study Group, Pediatric, 2000: 105: 295. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), Randomized, Controlled Trial, I Primary Outcomes
2. Horbar, Clark, and Lucey, Pediatrics: 1980:66:848: The Newborn Oxygram: Automated Processing of Transcutaneous Data
3. Long, Philip, and Lucey: Pediatrics, 1980:65:203,Excessive Handling as a Cause of Hypoxemia
4. Chow et al, Pediatrics: 2003, 111:339. Can Changes in Clinical Practice decrease the Incidence of Severe Retinopathy of Prematurity in Very Low Birth Weight Infants.
5. Tin et al, Arch Dis Child, Fetal Neonatal Ed: 2001: 84:F106. Pulse Oximetry, severe Retinopathy, and outcome at one year in babies of less than 28 weeks gestation
6. Schulze et al, J Pediatrics:1995: 126: 777. Effect of the arterial oxygenation level on cardiac output, oxygen extraction, and oxygen consumption in low birth weight infants receiving mechanical ventilation.

7. Askie et al, Pediatric Research: 2002; 51:378A The effect of differing oxygen saturation targeting ranges on long term growth and development of extremely preterm, oxygen dependent infants: The Boost Trial
8. ReLi Study: Unpublished work product of NICUQ 2000 ReLi Group.

Potential Benefits:

1. Reduction in ROP rates (measured by decreased Stage 3 and 4 disease, as well as decreased need for interventional surgery).
2. Reduction in Chronic lung disease (measured by decreased need for oxygen at 36 weeks PMA, decreased length of days in oxygen, and decreased length of hospital stay).

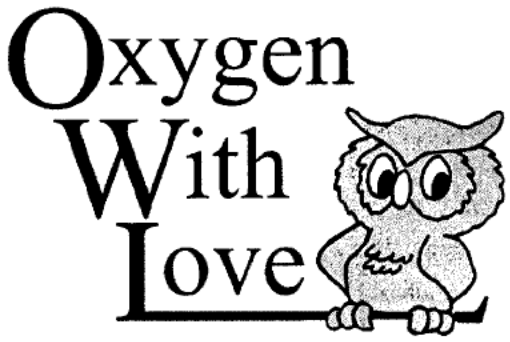
Potential Risks and costs:

1. Unrecognized system problems related to change in practice
   - Resistance to change-large effect on general practice techniques
   - Need for education on the varying requirements of Oxygen levels for the varying types of infants
   - False positives and response times
   - O2 Saturation Monitoring devices
2. Potential for poor growth, feeding intolerance, decreased physical activity, and decreased alertness in infants with established lung disease
3. Change in sleep patterns
3. Increased frequency of alarm rates leading to decreased compliance from staff.
4. No increase in costs, monitoring system already in place.
5. Increased mortality or morbidity from hypoxia.

How does the concept become operational?:

- Review the important parameters for oxygen saturation management for at risk babies.
- Develop goals for parameters of oxygen saturations.

- Establish an ICON to identify each infant at risk (**O**xygen **W**ith **L**ove)



- Develop a tool for monitoring compliance
- Educate the staff
- Do random walk through every 12 hours and document saturation level on at risk infants.
- Initiate plan and study compliance rate on a monthly basis

Person submitting this information:
Name: Margaret A. Thibodeaux
Institution: Ochsner Clinic Foundation

Oxygen With Love Worksheet-1st Year

	NAME	CL#	GEST	Birth Wt	Birth Dt	Ad Dt	Ad Wt	Ad. age	Vent	CPAP	O2	H. days	worst ROP	Surg	Birth PL	Apgars	Mat-Ster	Misc
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Oxygen With Love Worksheet-1st year

	NAME	CL#	GEST	Birth Wt	Birth Dt	Ad Dt	Ad Wt	Ad. age	Vent	CPAP	O2	H. days	worst ROP	Surg	Birth PL	Apgars	steroids	Misc
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Oxygen With Love Worksheet-2nd Year

	NAME	CL#	GEST	Birth Wt	Birth Dt	Ad Dt	Ad Wt	Ad. age	Vent	CPAP	O2	H. days	worst ROP	Surg	Birth PL	Apgars	steroids	Misc
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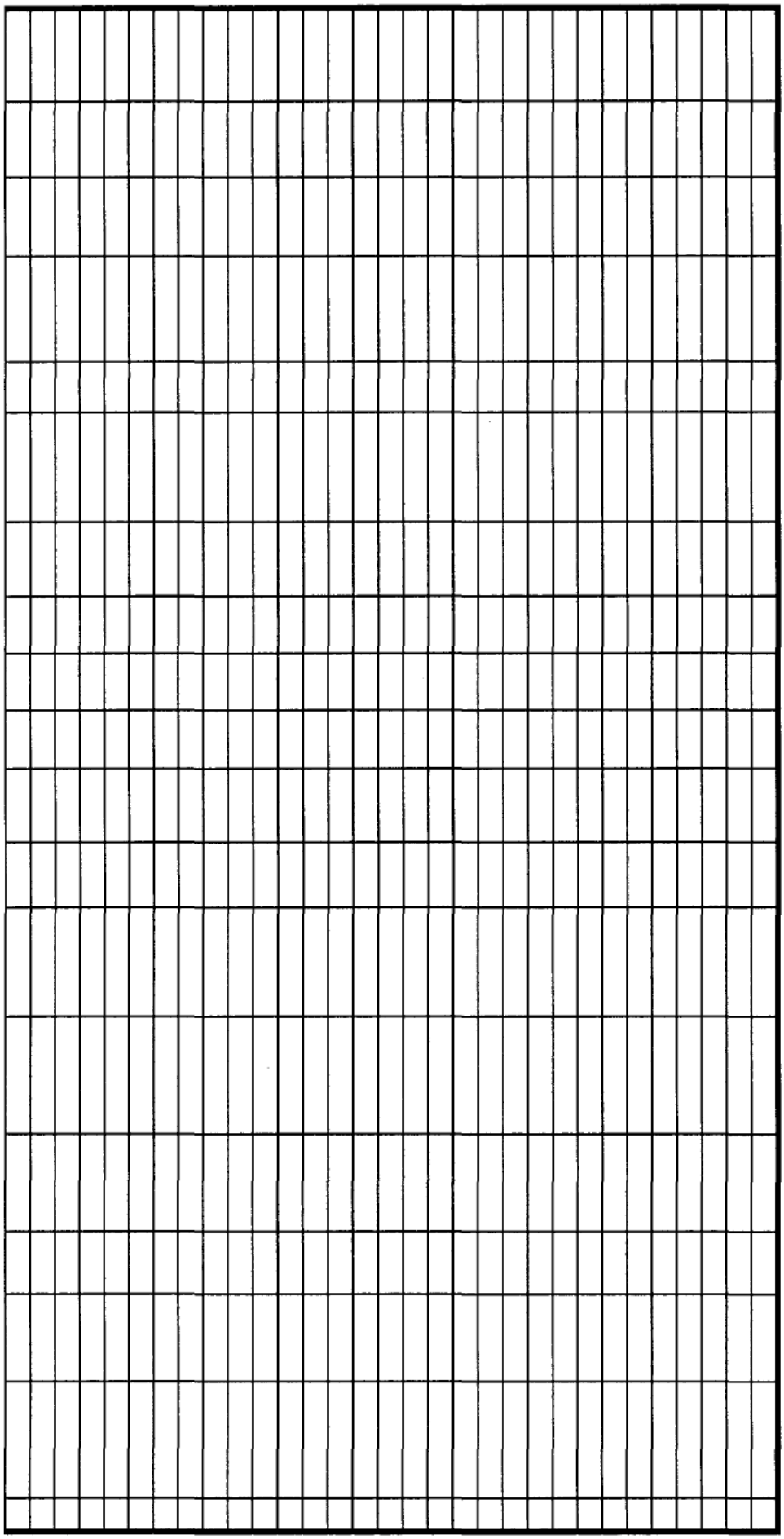
Oxygen With Love Worksheet-2nd Year

	NAME	CL#	GEST	Birth Wt	Birth Dt	Ad Dt	Ad Wt	Ad. age	Vent	CPAP	O2	H. days	worst ROP	Surg	Birth PL	Apgars	steroids	Misc
40																		
41																		
42																		
43																		



CONTRACT SUMMARY:

BASELINE FOR THE VLBW INFANT (birth weight 500-1500 g)

1. Set oxygen saturation monitor alarm limits at 80-95%.
2. Goal of saturations to be 85-93%.
3. Do not "TITRATE" FiO2 (risky to create extreme ups and downs in the infant's saturations.) Allow baby to fluctuate within the desired saturation parameters, making small movements up and down on FiO2 as needed.
4. Based on assessment, wean actively by 2-5% for saturations on the high side of parameters
5. Never increase the FiO2 without first assessing the baby.
6. If the need for increased FiO2 is sustained, the MD/NNP must be notified.
7. Document saturation levels and oxygen requirements clearly (as per unit policy)

When altering the oxygen being delivered stay with the infant until the saturations have stabilized within an acceptable range

Oxygen **W**ith **L**ove Worksheet

DATE																					
OWL#	NAME	D	N	D	N	D	N	D	N	D	N	D	N	D	N	D	N	D	N	D	N
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NEW ADMITS (Please but the name and the number of the OWL assigned)

NAME	DATE	OWL#	

Once a shift, at any time walk through the unit and document the actual sat on each baby w an OWL icon, if the sats are not correlating, document when they are

**If there is a new admit that weighs under 1500 gms and is o2 dependent-place baby on the program by getting an order and placing an OWL on their bed(OWL binder behind desk)

Comments(if out of range---Why?)(Is the baby on Room Air-off vent) or Greater than 1500 gms(babies on R/A but still on vent or C-PAP Should stay on protocol)

Please document reason for out of range if in disregard of protocol

For example-(alarm limits wrong;no response to alarms,etc)

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Trial Meeting
Date: Wednesday, December 14, 2005 11:57:47 AM

yep

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wed 12/14/2005 11:56 AM
To: Spong, Catherine (NIH/NICHD) [E]
Subject: Fw: SUPPORT Trial Meeting

Cathy
I will tell him that the DSMC chair has requested an in-person meeting. Ok?
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
CC: 'Avroy A. Fanaroff, M.D.' <aaf2@po.cwru.edu>; 'Betty Hastings' <bkh@rti.org>; Das, Abhik <adas@rti.org>; 'Ed Donovan' <Edward.Donovan@chmcc.org>; 'Ken Poole' <poo@rti.org>; 'Maynard Rasmussen' <Maynard.Rasmussen@sharp.com>; 'Michele' <mcw3@po.cwru.edu>; 'Neil Finer' <nfiner@ucsd.edu>; 'Shahnaz Duara' <sduara@miami.edu>; 'Wade Rich' <wrich@ucsd.edu>; 'Wally Carlo' <wcarlo@peds.uab.edu>
Sent: Wed Dec 14 11:36:09 2005
Subject: FW: SUPPORT Trial Meeting

Rose

I am very worried that such delays will have a large negative impact on SUPPORT, and also for all the other similar trials.

Can we try a videoconference, combined with a Webcast or similar technology?

Thanks for considering this.

Neil

From: Thomson, Merran [mailto:merran.thomson@imperial.ac.uk]
Sent: Wednesday, December 14, 2005 7:57 AM
To: Webb, Robin E.
Cc: csd12@columbia.edu; milhil@u.washington.edu; poppoff@u.washington.edu; Simon, Malinda (NIH/NHLBI) [C]; (b) (6) [redacted]; cgleason@u.washington.edu; md511@columbia.edu; [SCRN] Willinger, Marian; rjb6j@hscmail.mcc.viriginia.edu; huntc@nhlbi.nih.gov; mcallen@jhmi.edu; nfiner@ucsd.edu; Das, Abhik; Poole, W. Kenneth
Subject: RE: SUPPORT Trial Meeting

Dear robin

I can make the 20th and anytime week of 23rd to 27th

Best wishes

Merran Thomson

Consultant Neonatologist

Chief of Service

Division of Paediatrics

5th Floor Hammersmith House

Hammersmith Hospital

Du Cane Road

London W12 0HS

PA Marianna Loizia Tel 020 8383 3270

Tel 020 8383 2471 (direct line) Fax 020 8740 8281

Switch 020 8383 1000 Bleep 4400

-----Original Message-----
From: Webb, Robin E. [mailto:rwebb@rti.org]
Sent: 14 December 2005 15:00
To: (b) (6) [redacted]; cgleason@u.washington.edu; md511@columbia.edu; [SCRN] Willinger, Marian; rjb6j@hscmail.mcc.viriginia.edu; huntc@nhlbi.nih.gov; mcallen@jhmi.edu; Thomson, Merran; nfiner@ucsd.edu; Das, Abhik; Poole, W. Kenneth
Cc: csd12@columbia.edu; milhil@u.washington.edu; poppoff@u.washington.edu; Simon, Malinda (NIH/NHLBI) [C]
Subject: SUPPORT Trial Meeting

As you know, Dr. Avery, Chair of the DSMC has requested a face-to-face meeting with the members to discuss the SUPPORT Trial. Therefore, we are inquiring about your availability to attend a one day meeting in DC. The dates being considered are January 9th, 10th, 11th, 20th or sometime the week of the 23rd - 27th.

Thank you very much for your time.

Robin Webb

RTI International
6110 Executive Blvd., Suite 902
Rockville, MD 20853
301-770-8204

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT Trial Meeting
Date: Wednesday, December 14, 2005 11:56:20 AM

FYI
-----Original Message-----
From: Webb, Robin E.
Sent: Wednesday, December 14, 2005 11:51 AM
To: Hastings, Betty J.
Subject: RE: SUPPORT Trial Meeting

Yes, Avery, Boyle, Hunt, and Gleason. So far, the 24th looks the best.

> -----Original Message-----
> **From:** Hastings, Betty J.
> **Sent:** Wednesday, December 14, 2005 11:40 AM
> **To:** Webb, Robin E.
> **Subject:** FW: SUPPORT Trial Meeting
>
> Hi Robin,
> Have you heard from anyone else?
> -----Original Message-----
> **From:** Neil Finer [mailto:nfiner@ucsd.edu]
> **Sent:** Wednesday, December 14, 2005 11:36 AM
> **To:** 'Rosemary Higgins'
> **Cc:** 'Avroy A. Fanaroff, M.D.'; Hastings, Betty J.; Das, Abhik; 'Ed Donovan'; Poole, W. Kenneth; 'Maynard Rasmussen'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
> **Subject:** FW: SUPPORT Trial Meeting
>
> Rose
> I am very worried that such delays will have a large negative impact on SUPPORT, and also for all the other similar trials.
> Can we try a videoconference, combined with a Webcast or similar technology?
> Thanks for considering this.
> Neil

From: Thomson, Merran [mailto:merran.thomson@imperial.ac.uk]
Sent: Wednesday, December 14, 2005 7:57 AM
To: Webb, Robin E.
Cc: csd12@columbia.edu; milhil@u.washington.edu; poppoff@u.washington.edu; Simon, Malinda (NIH/NHLBI) [C]; (b) (6) ; cgleason@u.washington.edu; md511@columbia.edu; [SCRN] Willinger, Marian; rjb6j@hscmail.mcc.viriginia.edu; huntc@nhlbi.nih.gov; mcallen@jhmi.edu; nfiner@ucsd.edu; Das, Abhik; Poole, W. Kenneth
Subject: RE: SUPPORT Trial Meeting

Dear robin

I can make the 20th and anytime week of 23rd to 27th
Best wishes

Merran Thomson
Consultant Neonatologist
Chief of Service
Division of Paediatrics
5th Floor Hammersmith House

Hammersmith Hospital
Du Cane Road
London W12 0HS
PA Marianna Loizia Tel 020 8383 3270
Tel 020 8383 2471 (direct line) Fax 020 8740 8281
Switch 020 8383 (b) (6) Bleep (b) (6)

-----Original Message-----
From: Webb, Robin E. [mailto:rwebb@rti.org]
Sent: 14 December 2005 15:00
To: [redacted]; cgleason@u.washington.edu; md511@columbia.edu; [SCRN] Willinger, Marian; rjb6j@hscmail.mcc.viriginia.edu; huntc@nhlbi.nih.gov; mcallen@jhmi.edu; Thomson, Merran; nfiner@ucsd.edu; Das, Abhik; Poole, W. Kenneth
Cc: csd12@columbia.edu; milhil@u.washington.edu; poppoff@u.washington.edu; Simon, Malinda (NIH/NHLBI) [C]
Subject: SUPPORT Trial Meeting

As you know, Dr. Avery, Chair of the DSMC has requested a face-to-face meeting with the members to discuss the SUPPORT Trial. Therefore, we are inquiring about your availability to attend a one day meeting in DC. The dates being considered are January 9th, 10th, 11th, 20th or sometime the week of the 23rd - 27th.

Thank you very much for your time.

Robin Webb
RTI International
6110 Executive Blvd., Suite 902
Rockville, MD 20853
301-770-8204

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Information and communication
Date: Tuesday, December 13, 2005 8:58:53 AM

Yes let's discuss this afternoon

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Spong, Catherine (NIH/NICHD) <spongc@dir49.nichd.nih.gov>
Sent: Tue Dec 13 08:57:19 2005
Subject: FW: Information and communication

Cathy
I received this email this am. This is in respect to the SUPPORT Trial being stopped and an email that was cc'd to Cynthia Cole. I spoke to Barbara about it because she is the PI at the Emory site (not because she is the chairman). I would like to discuss this with you this afternoon if you have time. I will re-forward you the email in question.
Sorry for all the trouble!
Rose

-----Original Message-----
From: Augusto Sola [mailto:augusto_sola@oz.ped.emory.edu]
Sent: Tuesday, December 13, 2005 8:35 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Barbara Stoll
Subject: Information and communication

Dear Dr Higgins,
On or about 12/8 Dr Stoll sent me a copy of an e-mail written by me, which she said made it to NIH and was forwarded to her.
I replied the same day to Dr Stoll in detail and I am not sure if you saw my response.
In any case, it is distressing to me that someone will take time to take my e-mail out of context and forward it to NIH, who knows with what objective/purpose. Actually, this procedure may fall outside of accepted ethical behavior and may be a violation of privacy (as written nowadays at the bottom of many e-mails, ..."
>This message is for the designated recipient only and may contain
>privileged or confidential information.
.....")
Be this as it may, in order to avoid misunderstandings or miscommunication I would like to respectfully request that if you have any questions about what I say or write you please contact me directly and not through the Department Chair. I will be more than willing to answer openly and directly any questions you may have.
Many Thanks
Sincerely
Augusto Sola

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Hastings, Betty J.
Subject: RE: DSMC minutes
Date: Monday, December 12, 2005 4:35:48 PM

Thanks. I won't post the DSMC minutes on the Web. The request from the coordinators was actually for an old DSMC mtg for phototherapy just to clarify.
Thanks for the in put,
Kris

Kristin Zaterka-Baxter, RN, BSN, CCRP

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7750
Fax: (919) 485-7762

kzaterka@rti.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, December 12, 2005 4:32 PM
To: Das, Abhik; Zaterka-Baxter, Kristin
Cc: Hastings, Betty J.
Subject: RE: DSMC minutes

It may not be a good idea as some of the PDFs could be downloaded and sent via email. (this could have repercussions) They have what they need (IRB memo).
Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, December 12, 2005 4:27 PM
To: Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Hastings, Betty J.
Subject: RE: DSMC minutes

We usually dont share unedited DSMC minutes with the sites. However, for the SUPPORT study, if this is for documents that we have already sent to the PIs and coordinators, then I dont see any harm in putting them up on the private section of the website.

From: Zaterka-Baxter, Kristin
Sent: Monday, December 12, 2005 4:24 PM
To: Das, Abhik
Cc: 'higginsr@mail.nih.gov'; Hastings, Betty J.
Subject: DSMC minutes

Hi
Just wanted to solicit your thoughts on posting the DSMC minutes on the private network website. We had a request from one of the coordinators to have them posted. These would be the minutes the sites need to submit to their respective IRBs.

Thanks,
Kris

Kristin Zaterka-Baxter, RN, BSN, CCRP

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7750
Fax: (919) 485-7762

kzaterka@rti.org

From: Alan Jobe
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT TRIAL
Date: Monday, December 12, 2005 4:12:14 PM

Bloody hell – what is so complex! I thought the responses were rather clear. Do they need a consultant there to sort out the problems –I suggest that the PI be present to answer questions/misconceptions. The NICHD DMSC's have been overenthusiastic about stopping trials.

--

Alan H Jobe MD Phd
Prof of Pediatrics/Neonatology
Cincinnati Childrens Hospital
3333 Burnet Ave, Cincinnati OH, 45229
Ph - 5136368563
Fax - 5136368691
Alan.jobe@cchmc.org

From: Michele Walsh
To: Avroy A. Fanaroff; nfiner@ucsd.edu; "Avroy A. Fanaroff M.D."; "Betty Hastings"; "Das Abhik"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Maynard Rasmussen"; "Michele"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Subject: Re: RE:
Date: Monday, December 12, 2005 3:58:18 PM

Case infants were not eligible for SUPPORT largely bc delivered too soon after admission, although some may have declined the trial. MW

----- Original Message -----
From: Avroy A. Fanaroff
To: nfiner@ucsd.edu ; 'Avroy A. Fanaroff M.D.' ; 'Betty Hastings' ; 'Das Abhik' ; 'Ed Donovan' ; higginsr@mail.nih.gov ; 'Ken Poole' ; 'Maynard Rasmussen' ; 'Michele' ; 'Shahnaz Duara' ; 'Wade Rich' ; 'Wally Carlo'
Sent: Sunday, December 11, 2005 4:59 PM
Subject: RE:

The slides are pretty as well as informative
I would add to the slide that the Case Infants had similar criteria but were not randomized for various reasons - mainly parental refusal I believe but Michele can correct me.

Median SpO2 in healthy preterm infants = 97% (Ng et al Arch Dis Child 1998;79:F64) - I presume this is in room air and would so state.

Thanks
Av

-------*Original Message*-------

From: Neil Finer
Date: 12/11/05 16:01:04
To: nfiner@ucsd.edu; 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Das, Abhik'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Maynard Rasmussen'; 'Michele'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'

Subject: RE:

Hi Betty and Rose and Everyone

I am sorry to keep modifying our response but I want our presentation to be tight, factual, and convincing. I would like this PowerPoint presentation to be sent to the DSMC for the call on Tuesday. I will use this in the time allocated to me – I can do this in 15 minutes leaving lots of time for questions. If you feel that any of the additional analyses should also be sent to them, these are attached.

Please let me know if you find any errors – I have reviewed it so often it is all beginning to blur!

Be well

Neil

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Data Monitoring Committee
Date: Monday, December 12, 2005 1:06:08 PM

Hard to do this by email-(b) (5) [redacted]

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Spong, Catherine (NIH/NICHD) <spongc@dir49.nichd.nih.gov>
Sent: Mon Dec 12 13:04:34 2005
Subject: RE: Data Monitoring Committee

(b) (5) [redacted]

Rose

-----Original Message-----
From: Spong, Catherine (NIH/NICHD) [E]
Sent: Monday, December 12, 2005 1:04 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Data Monitoring Committee

Sounds good
(b) (5) [redacted]

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Spong, Catherine (NIH/NICHD) <spongc@dir49.nichd.nih.gov>
Sent: Mon Dec 12 13:01:29 2005
Subject: RE: Data Monitoring Committee

Does this sound ok??

(b) (5) [redacted]

Thanks you for your candor and I look forward to speaking with you.

Rose

-----Original Message-----

From: ckr3+@pitt.edu [mailto:ckr3+@pitt.edu]
Sent: Monday, December 12, 2005 9:42 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Data Monitoring Committee

Dear Dr. Higgins,

This e-mail is to notify you of my resignation as a member of the Data Safety Monitoring Committee for the NICHD NICU Trials.

I have been a member of the committee for more than ten years. As the only biostatistician on the committee in recent years, I have had a number of concerns about changes in the operating procedures for the committee in recent years and whether we are able to perform our role appropriately and effectively. It has been several years since we have had a face to face meeting although there have been a number of changes in the committee members. Teleconference meetings have not incorporated or facilitated in depth discussions important for the committee functioning, particularly in reviewing the protocols and consent forms for matters relating to the protection of safety of the subjects, recommendations for frequency and information to be provided for interim monitoring, and other major aspects of fulfilling our charge. It is also my understanding that we are advisory to the institute which may choose to accept or decline our recommendations.

The response to our recommendations regarding the SUPPORT Trial exemplify some of the issues that concern me. I will be happy to discuss my concerns with you in more detail if you wish, but do not have time this morning to do so.

With respect to the SUPPORT Trial, it is unfortunate that there will be no independent DMC biostatistician participating in the conference call since our initial recommendations and the information provided clearly involve important statistical considerations. When the conference call was scheduled, I indicated that I was not available until the latter part of the week. I am currently attending the meeting of the American Public Health Association in Philadelphia, with a prior commitment to a session at the same time that the conference call is scheduled. When I questioned the scheduling, I was told that I could read the information and provide any comments to the chair in advance. Although I have reviewed the materials and have some initial impressions, major biostatistical issues can only be addressed appropriately through participation in the meeting in collaboration with other members' expertise. I encourage that an independent biostatistician be found for the committee as soon as possible and that biostatistical expertise be fully integrated in review and decisions. During the early years of my participation, we had two biostatisticians on the committee, which provided an opportunity for back-up should one of us be unavailable; perhaps the committee could include two biostatisticians.

Dr. Avery has always provided very excellent and capable leadership of the DMC. It has been my pleasure to serve on the committee during his tenure as chair.

Please do not hesitate to contact me if you have any questions or would like to discuss the reasons for my resignation further.

Sincerely,

Carol Redmond

Dr. Carol K. Redmond
Distinguished Service Professor of Public Health
318A Parran Hall, University of Pittsburgh
Pittsburgh, PA 15261
Telephone: 1-412-624-1319 Fax: 1-412-624-2183

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Data Monitoring Committee
Date: Monday, December 12, 2005 1:04:50 PM

If (b) (5) .

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Spong, Catherine (NIH/NICHD) <spongc@dir49.nichd.nih.gov>
Sent: Mon Dec 12 13:02:23 2005
Subject: RE: Data Monitoring Committee

I think the (b) (5)

Thanks
Rose

-----Original Message-----
From: Spong, Catherine (NIH/NICHD) [E]
Sent: Monday, December 12, 2005 1:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Data Monitoring Committee

Probably should (b) (5)

Does that help?

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Spong, Catherine (NIH/NICHD) <spongc@dir49.nichd.nih.gov>
Sent: Mon Dec 12 12:54:19 2005
Subject: RE: Data Monitoring Committee

(b) (5)

We will get them together as soon as we can, but I suspect it will take 1-2 months (at least).

Thanks so much for your help!
Rose

-----Original Message-----
From: Spong, Catherine (NIH/NICHD) [E]
Sent: Monday, December 12, 2005 12:50 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Data Monitoring Committee

That sounds perfect
(b) (5)
[redacted]?

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Spong, Catherine (NIH/NICHD) <spongc@dir49.nichd.nih.gov>
Sent: Mon Dec 12 12:49:03 2005
Subject: RE: Data Monitoring Committee

Abhik spoke to Gordon Avery who agrees that we need (b) (5)
[redacted]
Any other suggestions?
Rose

-----Original Message-----
From: Spong, Catherine (NIH/NICHD) [E]
Sent: Monday, December 12, 2005 12:30 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Data Monitoring Committee

Oooh
We need to discuss and figure out strategy

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Spong, Catherine (NIH/NICHD) <spongc@dir49.nichd.nih.gov>
Sent: Mon Dec 12 09:49:51 2005
Subject: FW: Data Monitoring Committee

Cathy
See note below - any suggestions?
Thanks
Rose

-----Original Message-----
From: ckr3+@pitt.edu [mailto:ckr3+@pitt.edu]
Sent: Monday, December 12, 2005 9:42 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Data Monitoring Committee

Dear Dr. Higgins,

This e-mail is to notify you of my resignation as a member of the Data Safety Monitoring Committee for the NICHD NICU Trials.

I have been a member of the committee for more than ten years. As the only biostatistician on the committee in recent years, I have had a number of concerns about changes in the operating procedures for the committee in recent years and whether we are able to perform our role appropriately and effectively. It has been several years since we have had a face to face meeting although there have been a number of changes in the committee members. Teleconference meetings have not incorporated or facilitated in depth discussions important for the committee functioning, particularly in reviewing the protocols and consent forms for matters relating to the protection of safety of the subjects, recommendations for frequency and information to be provided for interim monitoring, and other major aspects of fulfilling our charge. It is also my understanding that we are advisory to the institute which may choose to accept or decline our recommendations.

The response to our recommendations regarding the SUPPORT Trial exemplify some of the issues that concern me. I will be happy to discuss my concerns with you in more detail if you wish, but do not have time this morning to do so.

With respect to the SUPPORT Trial, it is unfortunate that there will be no independent DMC biostatistician participating in the conference call since our initial recommendations and the information provided clearly involve important statistical considerations. When the conference call was scheduled, I indicated that I was not available until the latter part of the week. I am currently attending the meeting of the American Public Health Association in Philadelphia, with a prior commitment to a session at the same time that the conference call is scheduled. When I questioned the scheduling, I was told that I could read the information and provide any comments to the chair in advance. Although I have reviewed the materials and have some initial impressions, major biostatistical issues can only be addressed appropriately through participation in the meeting in collaboration with other members' expertise. I encourage that an independent biostatistician be found for the committee as soon as possible and that biostatistical expertise be fully integrated in review and decisions. During the early years of my participation, we had two biostatisticians on the committee, which provided an opportunity for back-up should one of us be unavailable; perhaps the committee could include two biostatisticians.

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Please do not hesitate to contact me if you have any questions or would like to discuss the reasons for my resignation further.

Sincerely,

Carol Redmond

Dr. Carol K. Redmond
Distinguished Service Professor of Public Health
318A Parran Hall, University of Pittsburgh

Pittsburgh, PA 15261
Telephone: 1-412-624-1319 Fax: 1-412-624-2183

From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Data Monitoring Committee
Date: Monday, December 12, 2005 12:13:36 PM

Has Avery seen this?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, December 12, 2005 11:31 AM
To: Willinger, Marian (NIH/NICHD)
Subject: FW: Data Monitoring Committee

-----Original Message-----
From: ckr3+@pitt.edu [mailto:ckr3+@pitt.edu]
Sent: Monday, December 12, 2005 9:42 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Data Monitoring Committee

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any comments to the chair in advance. Although I have reviewed the materials and have some initial impressions, major biostatistical issues can only be addressed appropriately through participation in the meeting in collaboration with other members' expertise. I encourage that an independent biostatistician be found for the committee as soon as possible and that biostatistical expertise be fully integrated in review and decisions. During the early years of my participation, we had two biostatisticians on the committee, which provided an opportunity for back-up should one of us be unavailable; perhaps the committee could include two biostatisticians.

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Please do not hesitate to contact me if you have any questions or would like to discuss the reasons for my resignation further.

Sincerely,

Carol Redmond

Dr. Carol K. Redmond
Distinguished Service Professor of Public Health
318A Parran Hall, University of Pittsburgh
Pittsburgh, PA 15261
Telephone: 1-412-624-1319 Fax: 1-412-624-2183

From: Hastings, Betty J.
To: Hastings, Betty J.; ckr3+@pitt.edu; cgleason@u.washington.edu; gavery123@hotmail.com; D'Alton, Mary (NIH/NICHD); Willinger, Marian (NIH/NICHD) [E]; Hunt, Carl (NIH/NHLBI) [E]; mcallen@jhmi.edu; merran.thomson@ic.ac.uk; rjb6j@hscmail.mcc.virginia.edu; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Berberich, Mary Anne (NIH/NHLBI) [E]
Cc: csd12@columbia.edu; mck6@pitt.edu; milhil@u.washington.edu; poppoff@u.washington.edu; Simon, Malinda (NIH/NHLBI) [C]; Perez, Tania (NIH/NHLBI) [C]; Das, Abhik; Poole, W. Kenneth; Zaterka-Baxter, Kristin; Gantz, Marie
Subject: RE: SUPPORT Conference Call
Date: Monday, December 12, 2005 8:27:56 AM
Attachments: SUPPORT Trial Final DSMC Response - Dec 121.ppt

Attached for your review is a PowerPoint presentation that was prepared by Dr. Neil Finer. We are hoping that you will have an opportunity to review this presentation prior to the call tomorrow.

Thank you for all of your help in reviewing this Support Trial material. <<SUPPORT Trial Final DSMC Response - Dec 121.ppt>>

Betty

Dear DSMC Members,
The DSMC conference call, to discuss the SUPPORT study, has been scheduled for Tuesday, December 13, at 2:00pm EST. To join this call please **dial the toll free number 888-396(b) (6) and enter the numeric Passcode (b) (6) (# when prompted). (The USA Toll Number is +1-210-839-(b) (6).** The leader of the call is Dr. Abhik Das. The agenda, list of participants and material to be discussed will be sent by Fed-Ex on December 6th. Please let me know if you do not receive this material.

Thank you.
Betty

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 7709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
e-mail: bkh@rti.org

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

December 11 2005

Report of the DSMC Nov 2005

The DSMC expressed 2 concerns:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

Report of the DSMC Nov 2005

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Evidence for Current SpO2 Ranges

- **SUPPORT Trial alarm limits were chosen as those most currently utilized within the Network and consistent with current evidence.**
- **To maintain PaO2 between 40 and 90mmHg would require SpO2 alarms of 92.5% to 95% (Paky et al Acta Paediatr. 1995 Jun; 84(6):613-6.)**

Evidence for Current SpO2 Ranges

- **No current prospective studies that have evaluated actual durations of time at various SpO2 levels**
- **Median SpO2 in healthy preterm infants in room air = 97% (Ng et al Arch Dis Child 1998;79:F64)**
- **All published studies reported target ranges ie lower vs higher using High SpO2 limits -92% vs 95% for populations but did not present any data as to how well these target were adhered to.**
- **Sun et al compared units with upper limits of >95% with those of ≤ 95% (Ped Res 2002, 51:350A)**

Evidence for Current SpO2 Ranges

- **Tin et al reported units by the limits they set without any individual patient data (Tin et al Arch Dis Child 2001;84:F106)**
- **Another survey compared SpO2 limits > 98% with ≤ 98%, and early limits – first 2 weeks- of > 92% vs < 92% (Anderson Ped Res 2002;51:367A)**
- **Chow et al reported on a change of practice with lowering of the SpO2 limit and other changes – They did not provide any actual SpO2 data (Chow et al, Pediatr 2003;111:339)**
- **All of these studies suggested that lower SpO2 limits were associated with less ROP.**

Evidence for Current SpO2 Ranges

- **Prior to the initiation of SUPPORT – there were no data indicating the actual percent of time ELBW infants spend at different SpO2 values or ranges**
- **The design of the trial using oximeter downloads was unique and will provide this information based on a large prospective cohort**
- **This trial was also unique in collecting this data from 2 hours of age in acutely unstable ELBW infants until they are out of oxygen for 3 days.**

Response to DSMC

Safety Issue of SpO2>95%

Concern regarding safety issue of duration of SpO2 > 95%

- ✓ **The current best data utilizing actual oximeter data is from Hagadorn et al (PAS 2004 Abstract: Late Breaker)**
- ✓ **Evaluated 78 ELBW infants for 70 hours per week for the first 4 weeks of life**
- ✓ **Lower and upper SpO2 limits were 83% -92% and 92%-98%**
- ✓ **Median SpO2 = 95%**
- ✓ **Medians from SUPPORT Oximeter groups – 92% and 94%, and for infants only in oxygen for the entire day the medians are 91% vs 93%.**

Response to DSMC:
Safety Issue of SpO2>95%

- STOP-ROP high treatment infants spent 97% of time > 95%
- Case Western a current NRN Center – Current data from SUPPORT type ELBW infants – SpO2 > 95% for > 50% time
- SUPPORT Infants on room air – SpO2 > 95% from 46% to 69% of time

Response to DSMC:
Safety Issue of SpO2>95%

- **Additional analyses evaluated the duration of time at SpO2 values of 98%, 99% and 100% as these may represent very high PaO2 values**
- **Infants in SUPPORT in ROOM Air spend more time at these values than infants receiving oxygen – 32% - 38% versus 5%-6%**

SUPPORT Trial Actual Results

91% - 95% Room Air 85% - 89%

	%	Cum %	%	Cum%
98%	15.49%	77.15	13.65%	81.42
99%	12.94%	90.09	10.37%	91.79
100%%	9.91%	100.00	8.21%	100.00
Total	38.3%		32.2%	

91% - 95% Oxygen 85% - 89%

98%	3.51%	96.90	2.66%	97.23
99%	1.90%	98.80	1.60%	98.83
100%	1.20%	100.00	1.17%	100.00
Total	6.6%		5.4%	

Response to DSMC: Safety Issue of SpO2>95%

- **The actual algorithm for conversion of displayed versus actual values results in inability to create a whole value for each displayed value.**
- **The data evaluated by the DSMC had an overestimation of durations > 95% in view of the data assigned conversion values of decimal values at 95% and considered to be > 95%**
- **This represented greater than 6% of the initial calculated durations > 95% for the 91%-95% group**

Response to DSMC: Safety Issue of SpO2>95%

- **In an effort to provide better information regarding both high and low SpO2 values and avoid the problem with the re-conversion algorithm, we asked for analyses for durations > 96% and < 84% as these are values which do not require conversion and are always unaltered.**

Response to DSMC: Safety Issue of SpO2>95%

- ✘ Any calculations which incorrectly assigned infants on room air to be analyzed as receiving Oxygen would overestimate the durations > 95%
- ✘ Our data forms only reported 3 FiO2 data points daily for the first 14 days and then only a single daily value thereafter.
- ✘ Thus we were using oximeter data and assigning it based on these data points to determine the true days in oxygen
- ✓ Reanalysis based on assigning the infant to oxygen only if all 3 points for the day had an FiO2 > .21 showed markedly lower durations of SpO2 > 95% and greater than 96%

Response to DSMC: Safety Issue of SpO2>95%

Percent of time of spent at SpO2 < 84% and > 96% (RTI Analyses In Oxygen, Dec 2, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.30%	14.05%
> 96%	21.45%	15.47%

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **Further analyses including only infants on Oxygen at all 3 data points for a given day**

(RTI Analyses In Oxygen all 3 Points, Dec 5, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
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- **We believe that neither oximeter group in the SUPPORT trial is being exposed to excessive durations of SpO2 > 95% based on all currently available information and the actual SUPPORT Trial Data analyzed to date.**
- **Current analyses demonstrate that the highest duration of SpO2 > 95% was 22.9%, and > 96% was 12.5% using only infants known to be in oxygen for all 3 daily data points in the first 14 days of life.**
- **These values are previously unreported for such a population, and significantly less than the original data reviewed by the DSMC.**

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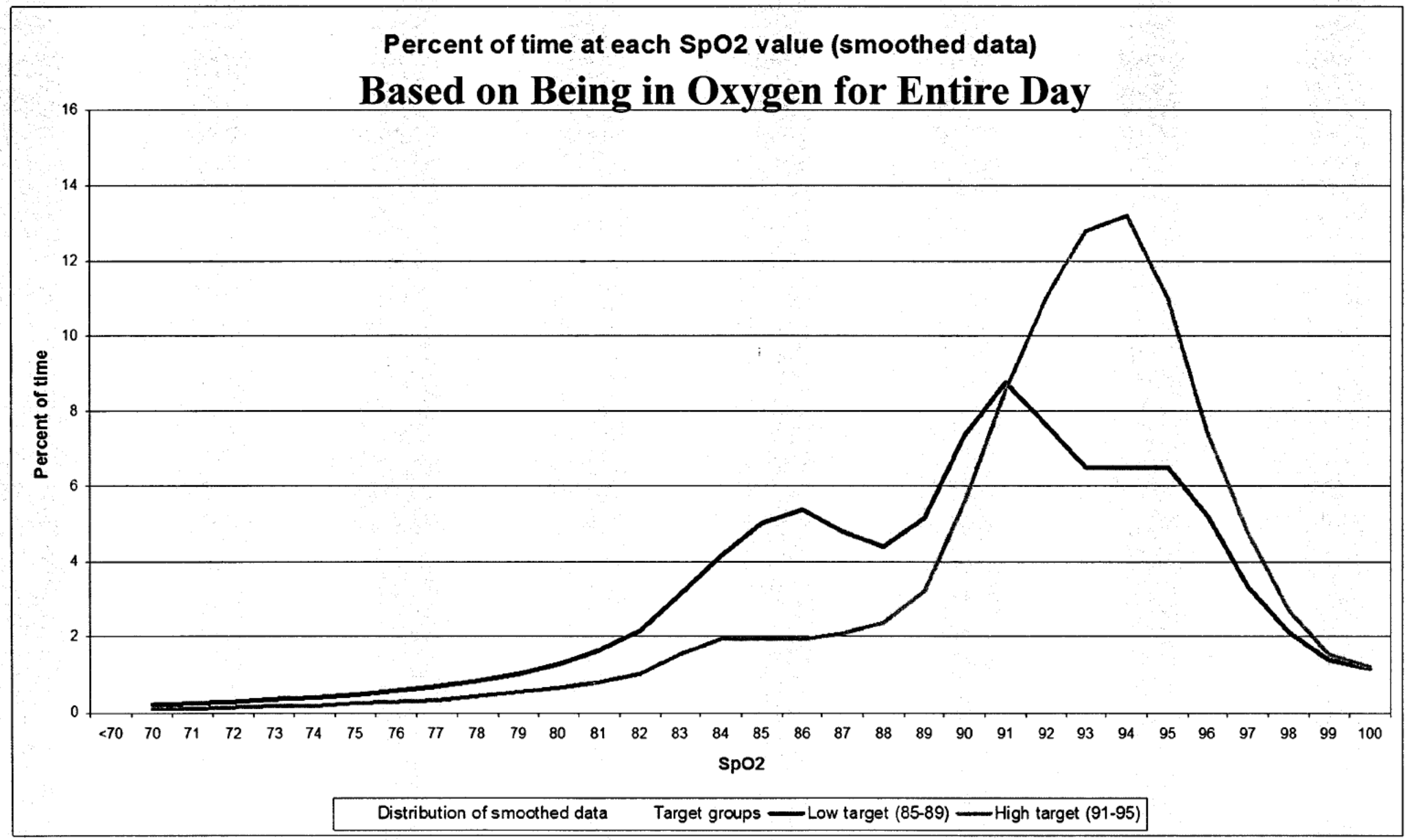

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- **The Actual time spent in Room Air during the first 14 days of life was 26.6% versus 35.5% for the 91%-95% group compared to the 85%-89% group.**
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- **The time in actual Target using only days when infants are in oxygen for all 3 data points**

91-95% = 55% 85% - 89% = 24.6%

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- **The 91% - 95% are more in target because their alarm sounds when they reach 95%**

✘ **The 85% - 89% are less time in target because when their SpO2 is > 89% (a reading of 93%) there is no alarm. The alarm only sounds at a reading of 95%**

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1. **Set high SpO2 limit – alarm to 94%. This will reduce the duration of SpO2 values > 95% for both groups, and should increase the time both groups spend in the narrow target range.**
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- **The SUPPORT Trial Committee and the Network Steering Committee appreciate the diligence and suggestions of the Data Safety Monitoring Committee**
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From: Neil Finer
To: "Neil Finer"; "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Das, Abhik"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Wade Rich"
Subject: RE: DSMC PowerPoint Presentation
Date: Sunday, December 11, 2005 11:05:54 PM
Attachments: SUPPORT Trial Final DSMC Response - Dec 12.ppt

Hi Betty
Av found another typo, and then so did I.
They are fixed in this version labeled Dec 12
Please circulate to the DSMC.
Many thanks
Neil

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Sunday, December 11, 2005 5:42 PM
To: 'Neil Finer'; 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Das, Abhik'; higginsr@mail.nih.gov; 'Ken Poole'; 'Wade Rich'
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Please let me know if you find any errors – I have reviewed it so often it is all beginning to blur!

Be well
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SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

December 11 2005

Report of the DSMC Nov 2005

The DSMC expressed 2 concerns:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

Report of the DSMC Nov 2005

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Evidence for Current SpO2 Ranges

- **SUPPORT Trial alarm limits were chosen as those most currently utilized within the Network and consistent with current evidence.**
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Safety Issue of SpO2>95%

Concern regarding safety issue of duration of SpO2 > 95%

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91% - 95% Room Air 85% - 89%

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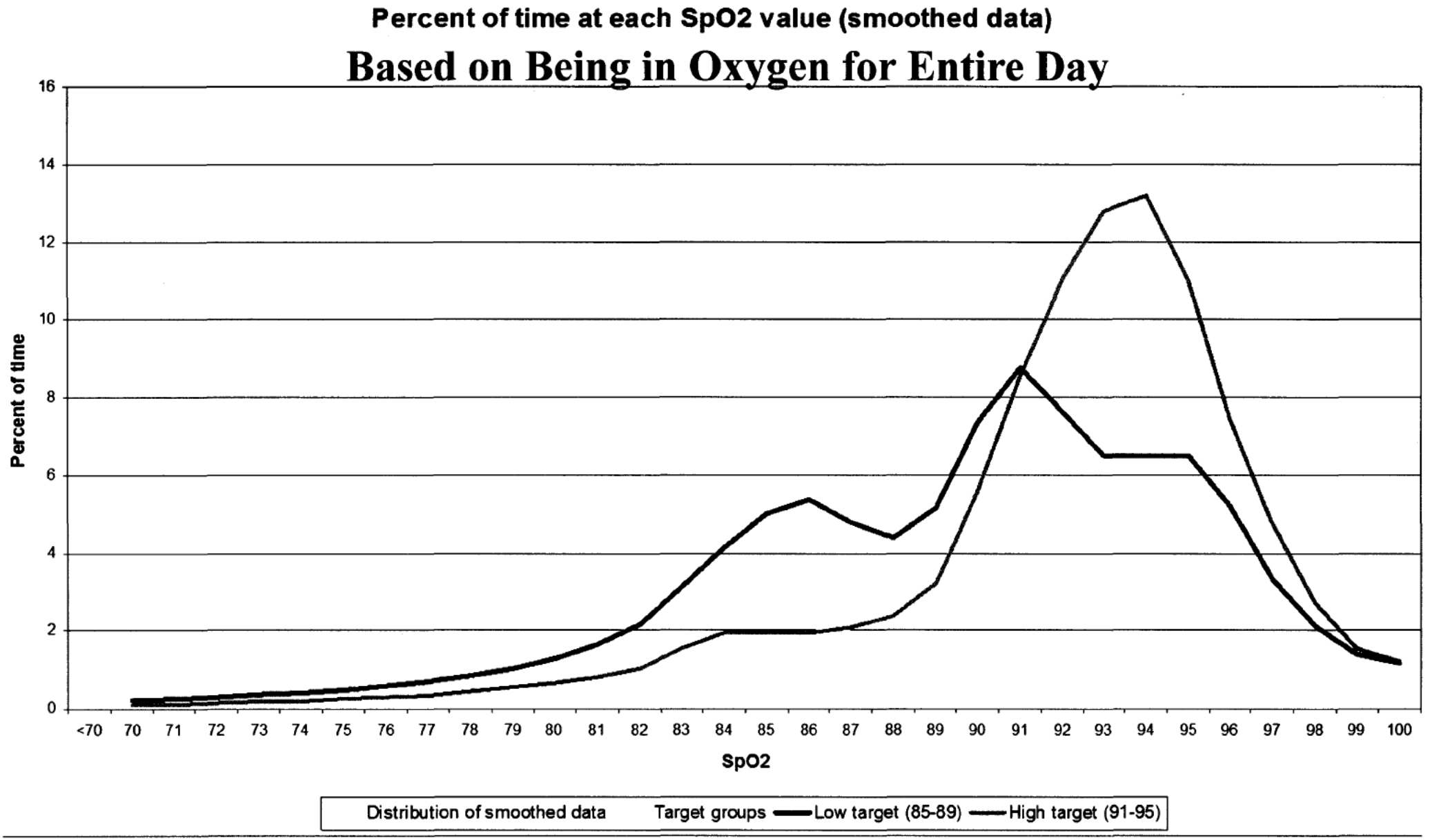

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To:	"Neil Finer"; "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Das, Abhik"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Wade Rich"
Subject:	RE:
Date:	Sunday, December 11, 2005 8:42:55 PM
Attachments:	SUPPORT Trial Final DSMC Response - Dec 11.ppt

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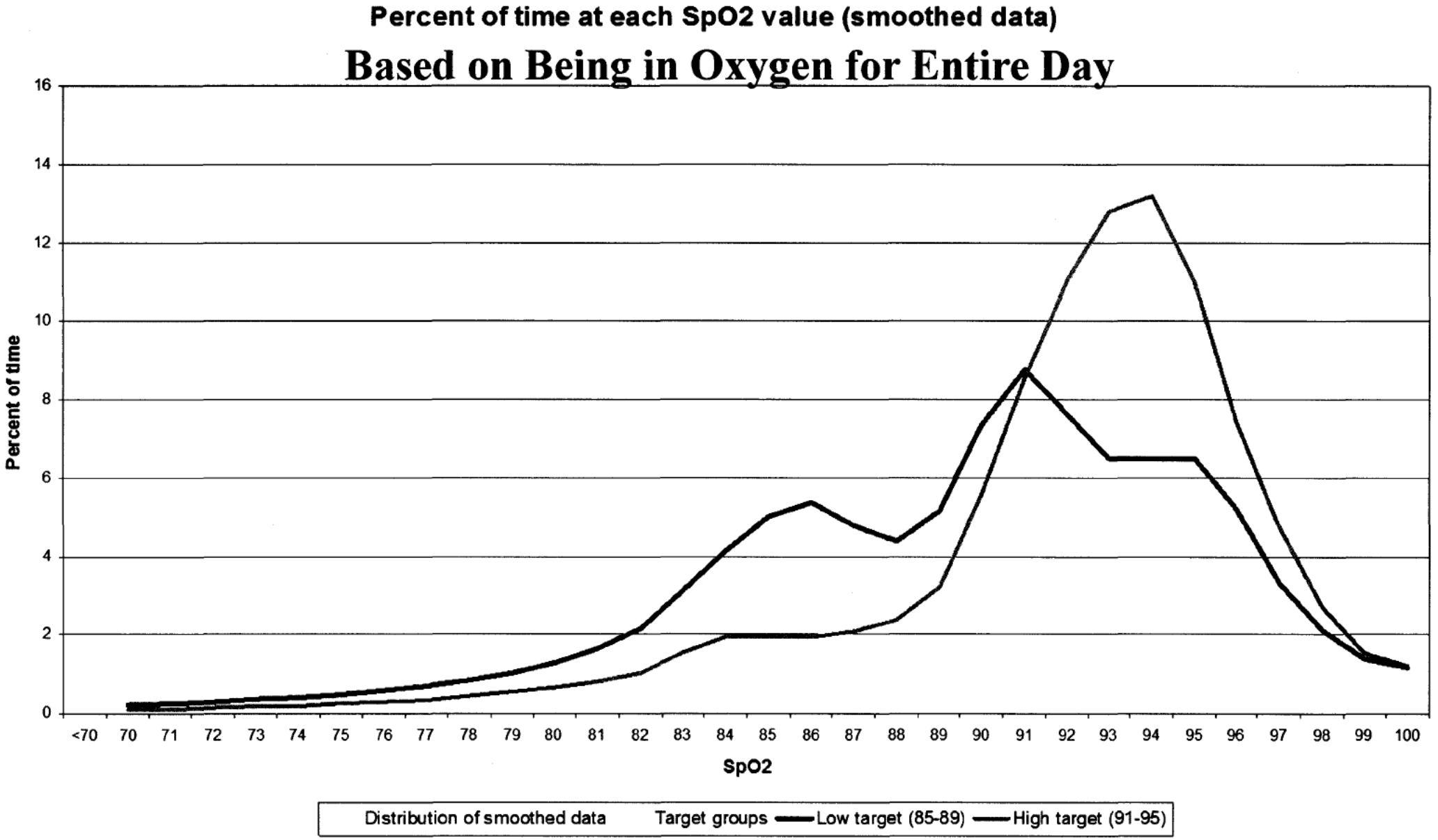
Range Assigned	High target (91-95)	Low target (85-89)
< 84%	6.40%	13.3%
> 96%	12.5%	9.39%

Response to DSMC: Safety Issue of SpO2>95%

- **We believe that neither oximeter group in the SUPPORT trial is being exposed to excessive durations of SpO2 > 95% based on all currently available information and the actual SUPPORT Trial Data analyzed to date.**
- **Current analyses demonstrate that the highest duration of SpO2 > 95% was 22.9%, and > 96% was 12.5% using only infants known to be in oxygen for all 3 daily data points in the first 14 days of life,.**
- **These values are previously unreported for such a population, and significantly less than the original data reviewed by the DSMC.**

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **An evaluation of the oximeter group data has revealed that there is a difference in the mean - 90% vs 92% and median values for the 2 groups – 92% vs 94%**
- **The Median SpO2s obtained using only days that were in oxygen at all 3 data points were 91% vs 93%**
- **These additional analyses have demonstrated that the cumulative time spent with an SpO2 of 90% or less is 22.80% (91% - 95%) versus 47.6% (85% - 89%) for a > 24% absolute difference between the groups.**



Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **We examined the actual FiO2 requirement of the infants in the Oximeter arms.**
- **If the algorithms were working as intended, then there should be a difference in the FiO2 requirement between the groups**

Response to DSMC:

Futility regarding Separation of Oximeter Groups

- **The Actual time spent in Room Air during the first 14 days of life was 26.6% versus 35.5% for the 91%-95% group compared to the 85%-89% group.**
- **These differences persisted for data beyond 14 days**
- **The 2 groups remained separated by at least 3% duration for FiO2s of $\leq$ 50%**

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **The time in actual Target using only days when infants are in oxygen for all 3 data points**

91-95% = 55% 85% - 89% = 24.6%

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **The 91% - 95% are more in target because their alarm sounds when they reach 95%**
- ✘ **The 85% - 89% are less time in target because when their SpO2 is > 89% (a reading of 93%) there is no alarm. The alarm only sounds at a reading of 95%**
- ✓ **We believe that we can improve this time in range by lowering the high alarm to 94%**

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **It is uncertain what duration of differences in either SpO2 of FiO2 will be associated with different short and long term outcomes, but we are achieving some separation in both to the present.**
- **We believe that greater separation is possible and desirable and have made a number of recommendations to ensure that this will occur.**

Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups

1. **Set high SpO2 limit – alarm to 94%. This will reduce the duration of SpO2 values > 95% for both groups, and should increase the time both groups spend in the narrow target range.**
2. **Require documentation that the oximeters alarm limits are set and functional as per protocol every 4-6 hours**
3. **Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect saturations measured while on oxygen therapy and exclude saturations of infants in room air**

Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups

4. Further training and in-service at all the sites to stress the importance of keeping the SpO2 alarms functional and at the limits of 85% and 95%. We will use the OWL (Oxygen with Love Program) developed at Oschner.
5. Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation
6. Place bedside cards to indicate the desired target range

Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups

7. **Initiate compliance monitoring visits coordinated by RTI to visit random sites**
8. **Reanalyze group differences after an additional 100-150 infants have been enrolled.**
9. **Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.**

Response to DSMC

- **The SUPPORT Trial Committee and the Network Steering Committee appreciate the diligence and suggestions of the Data Safety Monitoring Committee**
- **We trust that our response and suggestions to improve the SUPPORT Trial are found acceptable and that we may be allowed to continue this important trial.**

From:	Neil Finer
To:	nfiner@ucsd.edu; "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Das, Abhik"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Maynard Rasmussen"; "Michele"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Subject:	RE:
Date:	Sunday, December 11, 2005 4:01:21 PM
Attachments:	SUPPORT Trial DSMC Response - Final Dec 11.ppt Percent of time spent at each SpO2 value (FiO2 gt21) 12-5-05.doc Daily FiO2 for first 14 days.doc

Hi Betty and Rose and Everyone

I am sorry to keep modifying our response but I want our presentation to be tight, factual, and convincing. I would like this PowerPoint presentation to be sent to the DSMC for the call on Tuesday. I will use this in the time allocated to me – I can do this in 15 minutes leaving lots of time for questions. If you feel that any of the additional analyses should also be sent to them, these are attached.

Please let me know if you find any errors – I have reviewed it so often it is all beginning to blur!

Be well

Neil

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

December 11 2005

Report of the DSMC Nov 2005

The DSMC expressed 2 concerns:

1. **There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range**

Report of the DSMC Nov 2005

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Evidence for Current SpO2 Ranges

- **SUPPORT Trial alarm limits were chosen as those most currently utilized within the Network and consistent with current evidence.**
- **To maintain PaO2 between 40 and 90mmHg would require SpO2 alarms of 92.5% to 95% (Paky et al Acta Paediatr. 1995 Jun; 84(6):613-6.)**

Evidence for Current SpO2 Ranges

- No current prospective studies that have evaluated actual durations of time at various SpO2 levels
- Median SpO2 in healthy preterm infants = 97% (Ng et al Arch Dis Child 1998;79:F64)
- All published studies reported target ranges ie lower vs higher using High SpO2 limits -92% vs 95% for populations but did not present any data as to how well these target were adhered to.
- Sun et al compared units with upper limits of >95% with those of $\leq$ 95% (Ped Res 2002, 51:350A)

Evidence for Current SpO2 Ranges

- **Tin et al reported units by the limits they set without any individual patient data (Tin et al Arch Dis Child 2001;84:F106)**
- **Another survey compared SpO2 limits > 98% with ≤ 98%, and early limits – first 2 weeks- of > 92% vs < 92% (Anderson Ped Res 2002;51:367A)**
- **Chow et al reported on a change of practice with lowering of the SpO2 limit and other changes – They did not provide any actual SpO2 data (Chow et al, Pediatr 2003;111:339)**
- **All of these studies suggested that lower SpO2 limits were associated with less ROP.**

Evidence for Current SpO2 Ranges

- **Prior to the initiation of SUPPORT – there were no data indicating the actual percent of time ELBW infants spend at different SpO2 values or ranges**
- **The design of the trial using oximeter downloads was unique and will provide this information based on a large prospective cohort**
- **This trial was also unique in collecting this data from 2 hours of age in acutely unstable ELBW infants until there are out of oxygen**

Response to DSMC

Safety Issue of SpO2>95%

Concern regarding safety issue of duration of SpO2 > 95%

- ✓ **The current best data utilizing actual oximeter data is from Hagadorn et al (PAS 2004 Abstract: Late Breaker)**
- ✓ **Evaluated 78 ELBW infants for 70 hours per week for the first 4 weeks of life**
- ✓ **Lower and upper SpO2 limits were 83% -92% and 92%-98%**
- ✓ **Median SpO2 = 95%**
- ✓ **Medians from SUPPORT Oximeter groups – 92% and 94%, and for infants only in oxygen for the entire day the medians are 91% vs 93%.**

Response to DSMC:
Safety Issue of SpO2>95%

- STOP-ROP high treatment infants spent 97% of time > 95%
- Case Western a current NRN Center – Current data from SUPPORT type ELBW infants – SpO2 > 95% for > 50% time
- SUPPPORT Infants on room air – SpO2 > 95% from 46% to 69% of time

Response to DSMC:
Safety Issue of SpO2>95%

- **Additional analyses evaluated the duration of time at SpO2 values of 98%, 99% and 100% as these may represent very high PaO2 values**
- **Infants in SUPPORT in ROOM Air spend more time at these values than infants receiving oxygen – 32% - 38% versus 5%-6%**

SUPPORT Trial Actual Results

91% - 95% Room Air 85% - 89%

	%	Cum %	%	Cum%
98%	15.49%	77.15	13.65%	81.42
99%	12.94%	90.09	10.37%	91.79
100%%	9.91%	100.00	8.21%	100.00
Total	**38.3%**		**32.2%**	

91% - 95% Oxygen 85% - 89%

98%	3.51%	96.90	2.66%	97.23
99%	1.90%	98.80	1.60%	98.83
100%	1.20%	100.00	1.17%	100.00
Total	**6.6%**		**5.4%**	

Response to DSMC: Safety Issue of SpO2>95%

- **The actual algorithm for conversion of displayed versus actual values results in inability to create a whole value for each displayed value.**
- **The data evaluated by the DSMC had an overestimation of durations > 95% in view of the data assigned conversion values of decimal values at 95% and considered to be > 95%**
- **This represented greater than 6% of the initial calculated durations > 95% for the 91%-95% group**

Response to DSMC: Safety Issue of SpO2>95%

- **In an effort to provide better information regarding both high and low SpO2 values and avoid the problem with the re-conversion algorithm, we asked for analyses for durations > 96% and < 84% as these are values which do not require conversion and are always unaltered.**

Response to DSMC: Safety Issue of SpO2>95%

- ✘ Any calculations which incorrectly assigned infants on room air to be analyzed as receiving Oxygen would overestimate the durations > 95%
- ✘ Our data forms only reported 3 FiO2 data points daily for the first 14 days and then only a single daily value thereafter.
- ✘ Thus we were using oximeter data and assigning it based on these data points to determine the true days in oxygen
- ✓ Reanalysis based on assigning the infant to oxygen only if all 3 points for the day had an FiO2 > .21 showed markedly lower durations of SpO2 > 95% and greater than 96%

Response to DSMC: Safety Issue of SpO2>95%

Percent of time of spent at SpO2 < 84% and > 96% (RTI Analyses In Oxygen, Dec 2, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.30%	14.05%
> 96%	21.45%	15.47%

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **Further analyses including only infants on Oxygen at all 3 data points for a given day**

(RTI Analyses In Oxygen all 3 Points, Dec 5, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	6.40%	13.3%
≥ 96%	12.5%	9.39%

Response to DSMC: Safety Issue of SpO2>95%

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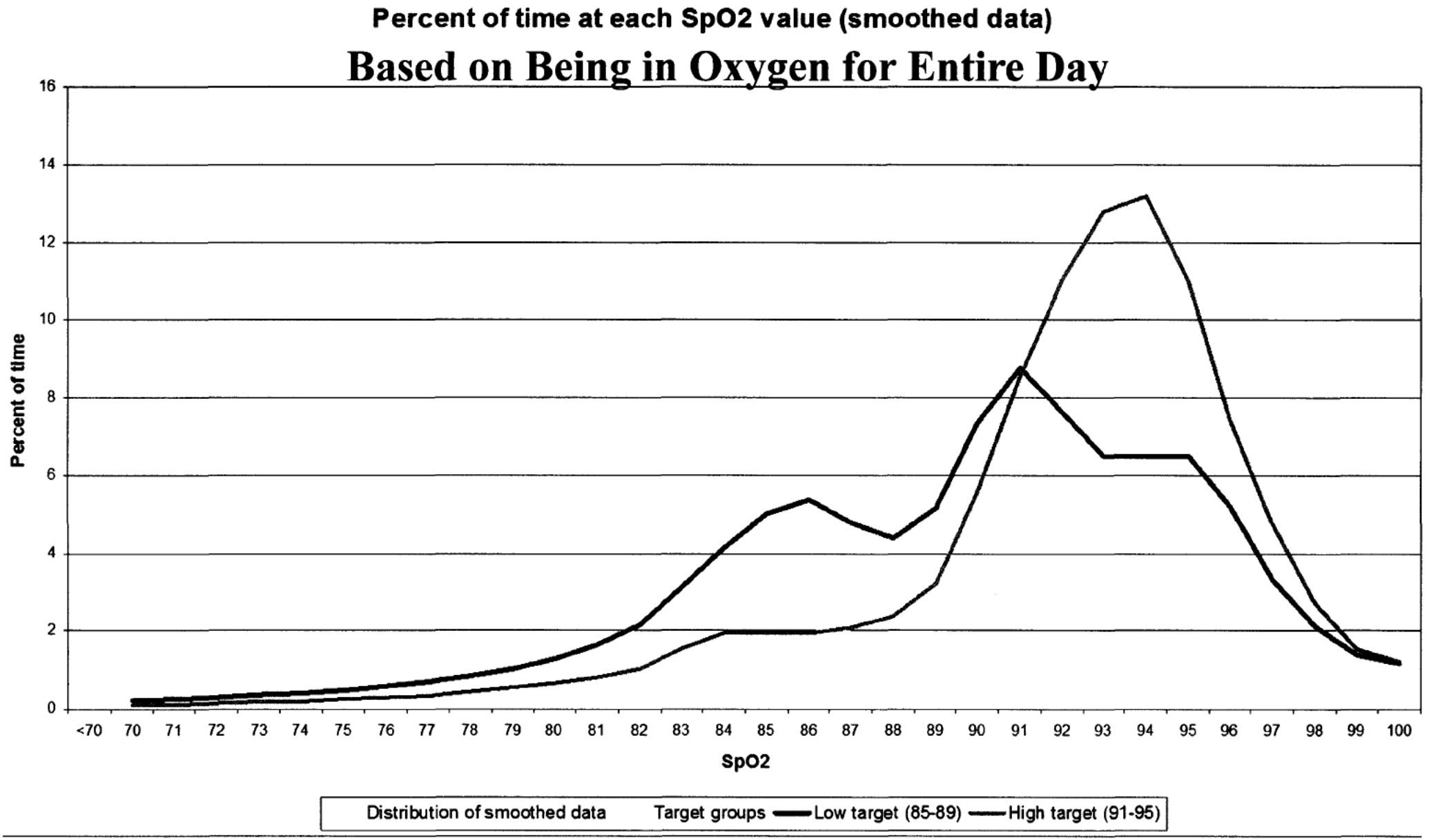

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Percent of time spent at each SpO2 value for infants with FiO2 > 0.21 at each of three timepoints recorded on SUPP05

Data processed as of 12/02/2005

Data included in tables and graphs

Infants included	High target (91-95)	Low target (85-89)	Total
Number	65	62	127
Hours	8703	7513	16216

Percent of time spent at each actual SpO2 value, by treatment group

	High target (91-95)		Low target (85-89)	
SpO2	Percent	Cumulative	Percent	Cumulative
<70	0.73	0.73	1.75	1.75
70	0.09	0.82	0.21	1.96
71	0.11	0.93	0.24	2.20
72	0.12	1.06	0.27	2.48
73	0.15	1.21	0.33	2.80
74	0.18	1.39	0.38	3.19
75	0.22	1.60	0.44	3.63
76	0.26	1.86	0.53	4.16
77	0.31	2.17	0.62	4.78
78	0.38	2.55	0.75	5.53
79	0.49	3.04	0.93	6.46
80	0.61	3.65	1.14	7.60
81	0.73	4.38	1.45	9.05
82	0.90	5.28	1.86	10.91
83	1.12	6.39	2.42	13.34
84	0.00	6.39	2.30	15.64
84.25	0.00	6.39	0.95	16.59
84.5	0.00	6.39	1.04	17.63
84.75	0.00	6.39	1.15	18.78
85	0.00	6.39	2.83	21.61
85.5	7.79	14.19	0.00	21.61
86	0.00	14.19	5.54	27.14
87	0.00	14.19	5.21	32.36
88	2.22	16.40	4.37	36.72
89	2.50	18.90	4.38	41.11
90	3.90	22.80	5.95	47.06
91	7.20	30.00	8.72	55.78
92	9.90	39.90	8.79	64.56
93	12.17	52.07	0.00	64.56
94	13.37	65.44	0.00	64.56
94.5	0.00	65.44	26.05	90.61
95	8.58	74.02	0.00	90.61
95.25	3.09	77.11	0.00	90.61
95.5	2.72	79.82	0.00	90.61
95.75	2.51	82.33	0.00	90.61
96	5.10	87.44	0.00	90.61
97	5.96	93.39	3.96	94.56
98	3.51	96.90	2.66	97.23
99	1.90	98.80	1.60	98.83
100	1.20	100.00	1.17	100.00

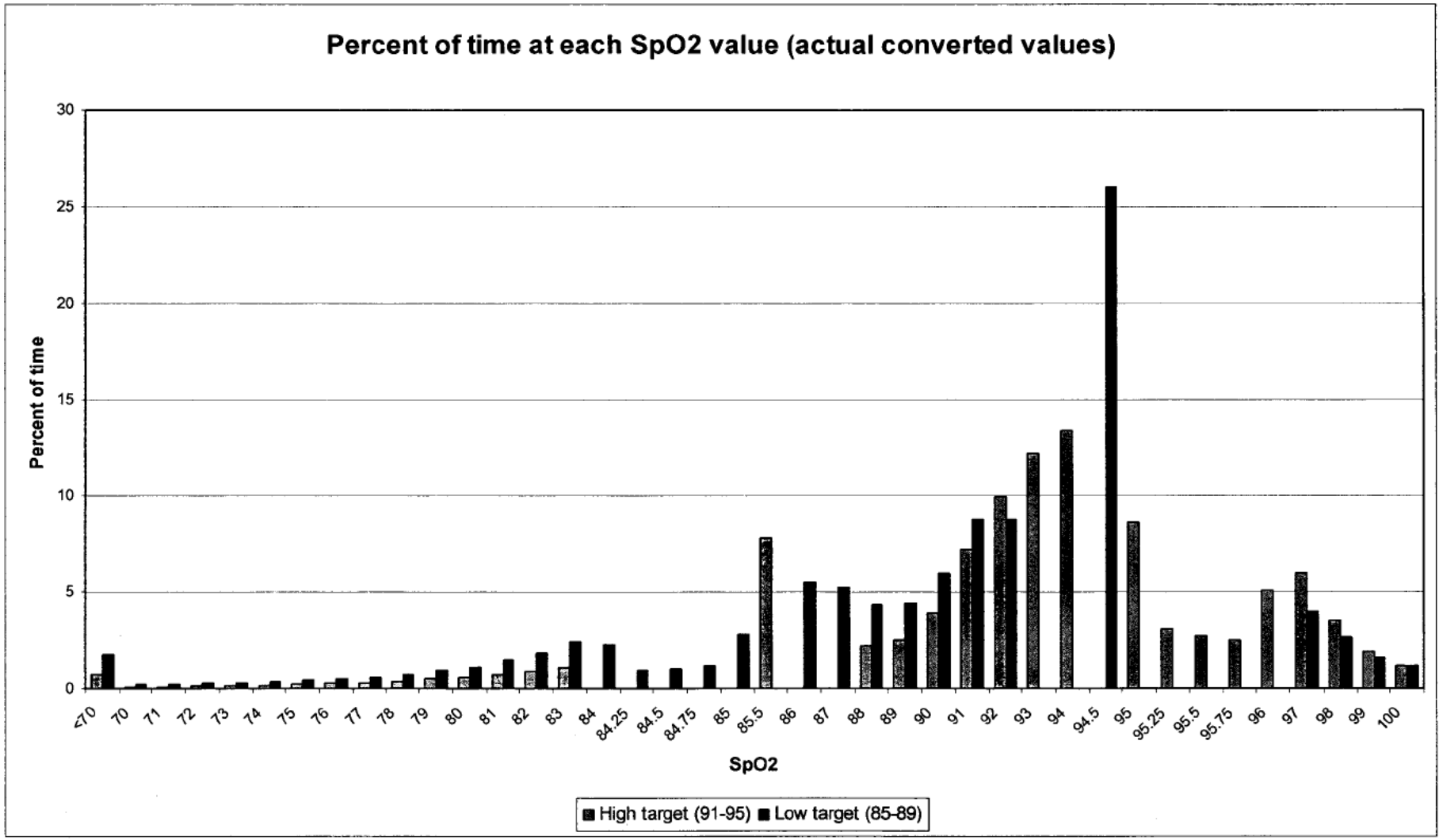
Median SpO2

	High target (91-95)	Low target (85-89)
Median	93	91

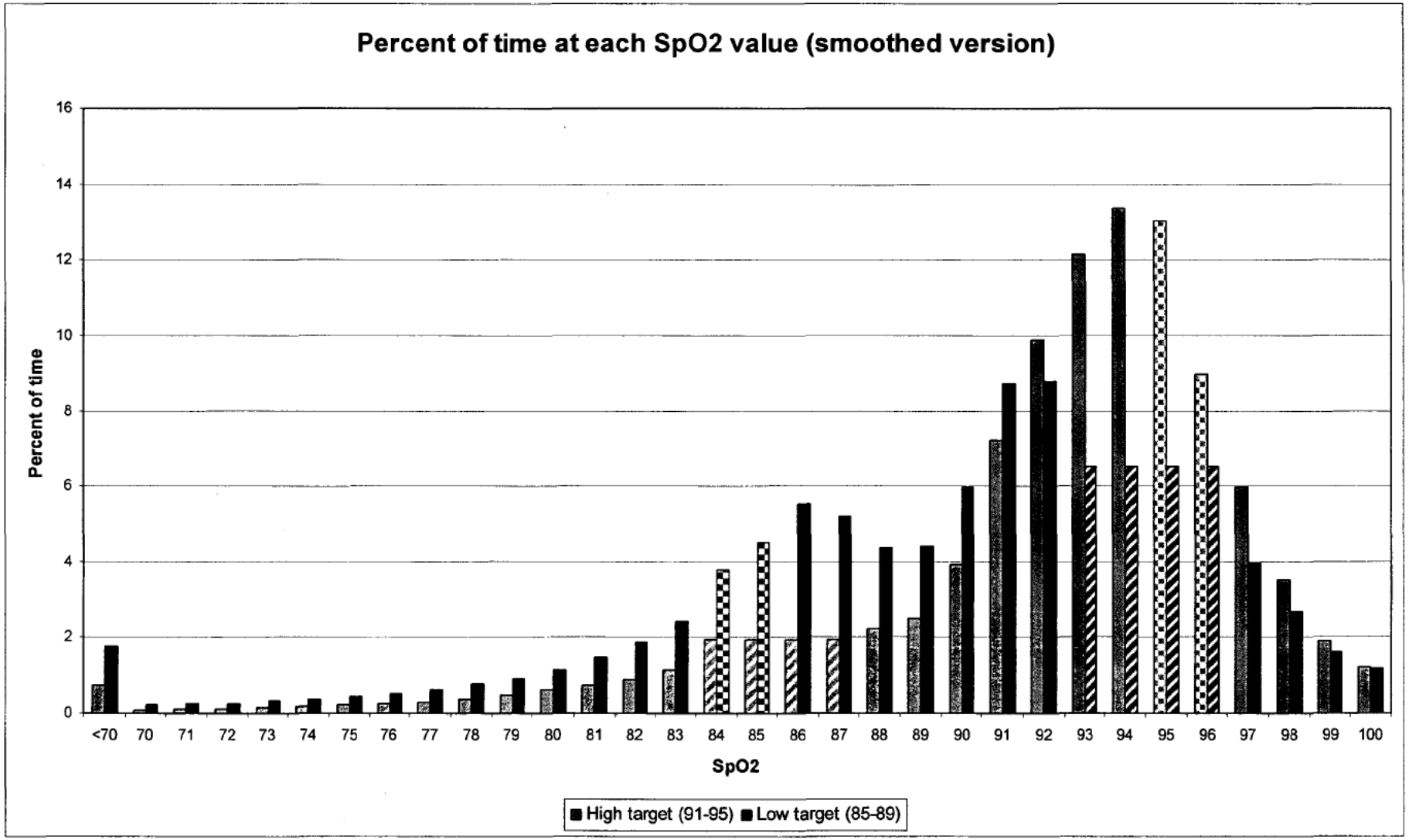
Percent of time of spent at SpO2 <84 and >96

Range	High target (91-95)	Low target (85-89)
<84	6.39	13.34
>96	12.56	9.39

The graph below displays each individual converted SpO2 value



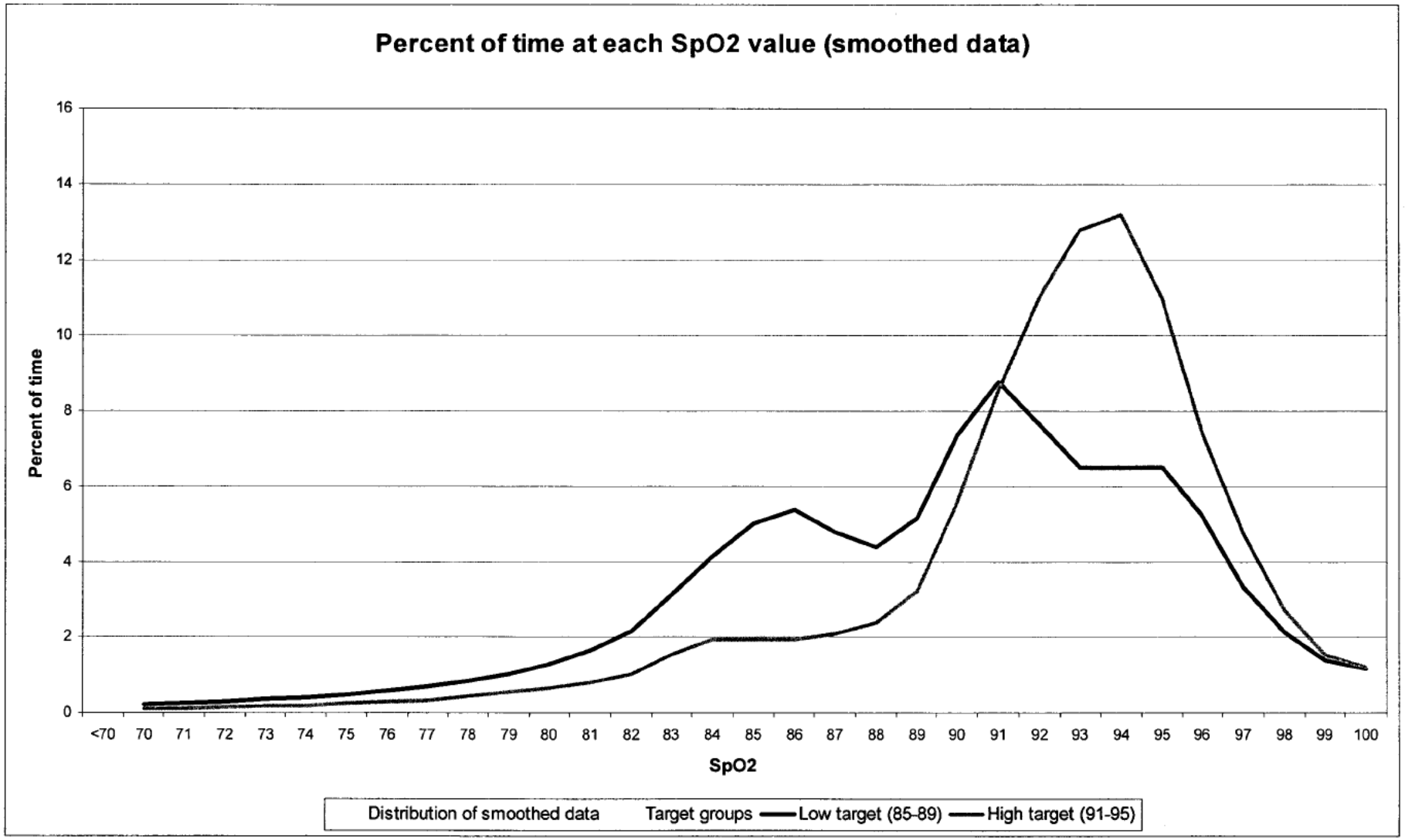
In the graph below, the converted SpO2 values have been smoothed to give a better idea of the distribution. Adjustments made to smooth the data are listed on the following page. Patterns are used to identify altered values.



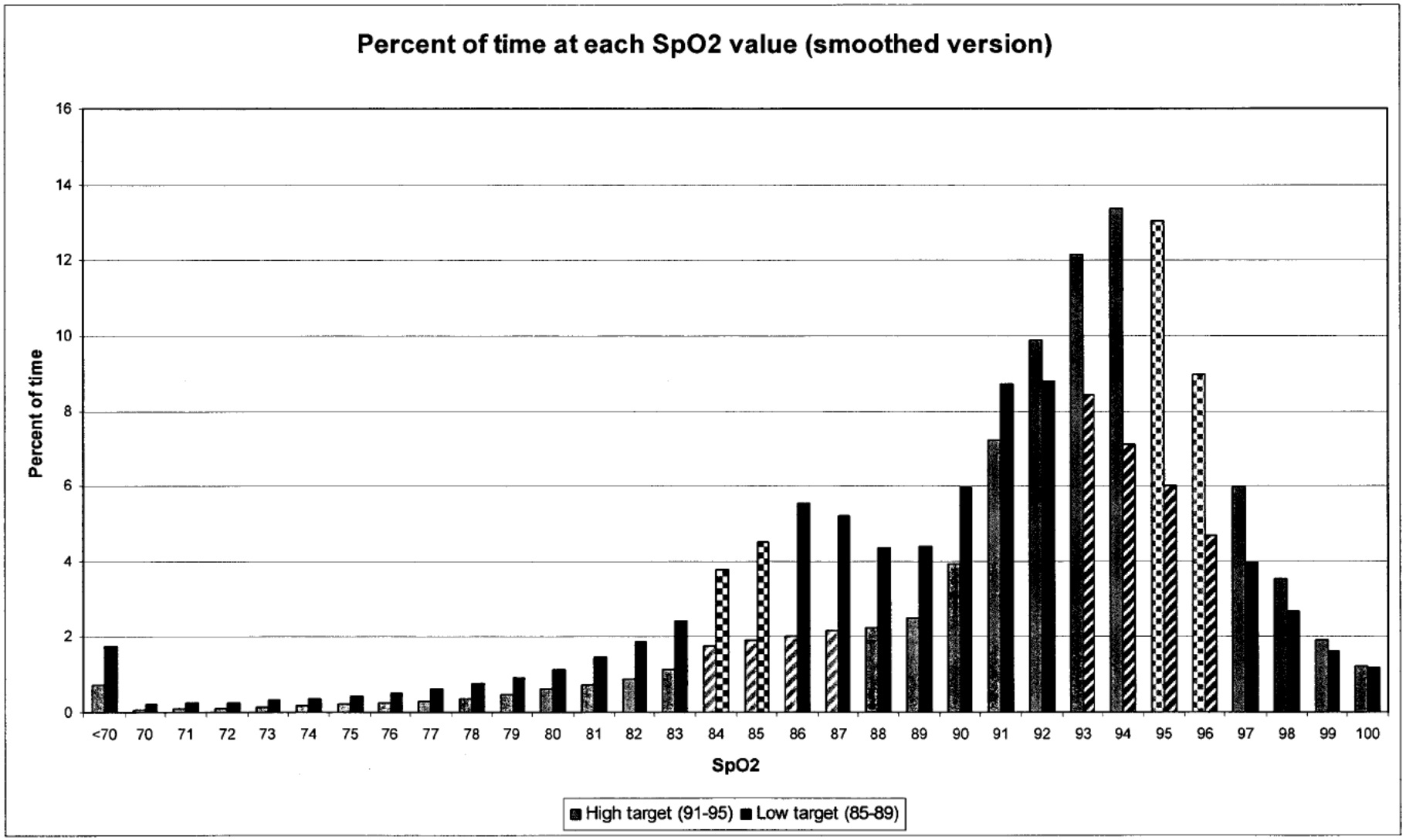
Changes made to achieve smoothing

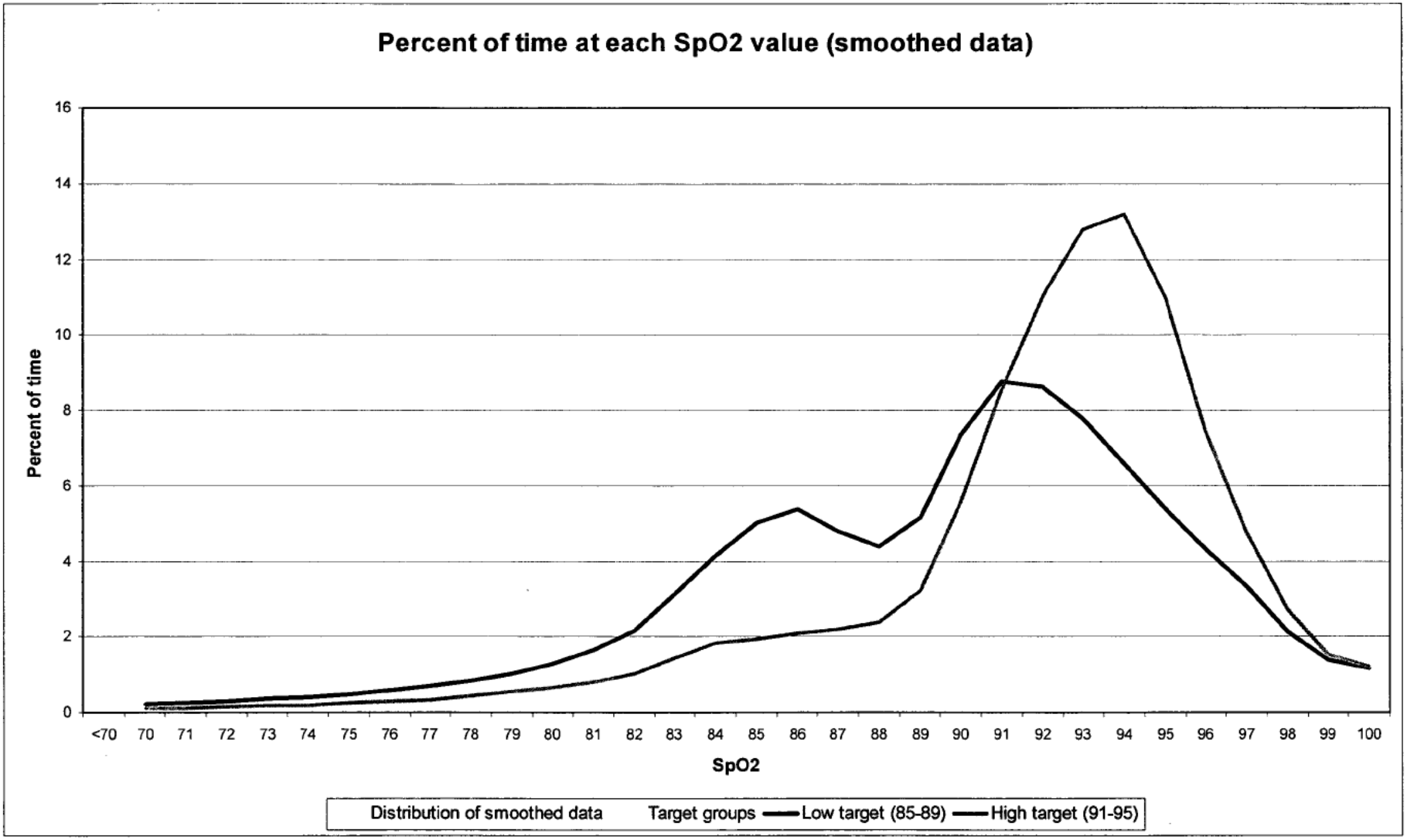
High target (91-95)	Pattern
Percent of time at converted value of 85.5 are spread evenly over 84-87	Blue diagonal stripes
Percent of time at 95 includes converted values of 95, 95.25 and half the percent of time at 95.5	Blue checked
Percent of time at 96 includes converted values of 96, 95.75 and half the percent of time at 95.5	Blue checked

Low target (85-89)	Pattern
Percent of time at converted value of 94.5 are spread evenly over 93-96	Burgundy diagonal stripes
Percent of time at 84 includes converted values of 84, 84.25 and half the percent of time at 84.5	Burgundy checked
Percent of time at 85 includes converted values of 85, 84.75 and half the percent of time at 84.5	Burgundy checked



The following two graphs are the result of some additional smoothing.





Daily FiO2 values for first 14 days of life
Average daily FiO2 for each infant (average of 3 FiO2 measurements on SUPP05)
Includes data on 155 infants (73 High target, 82 Low target) for whom pulse oximeter data is available
12-5-05

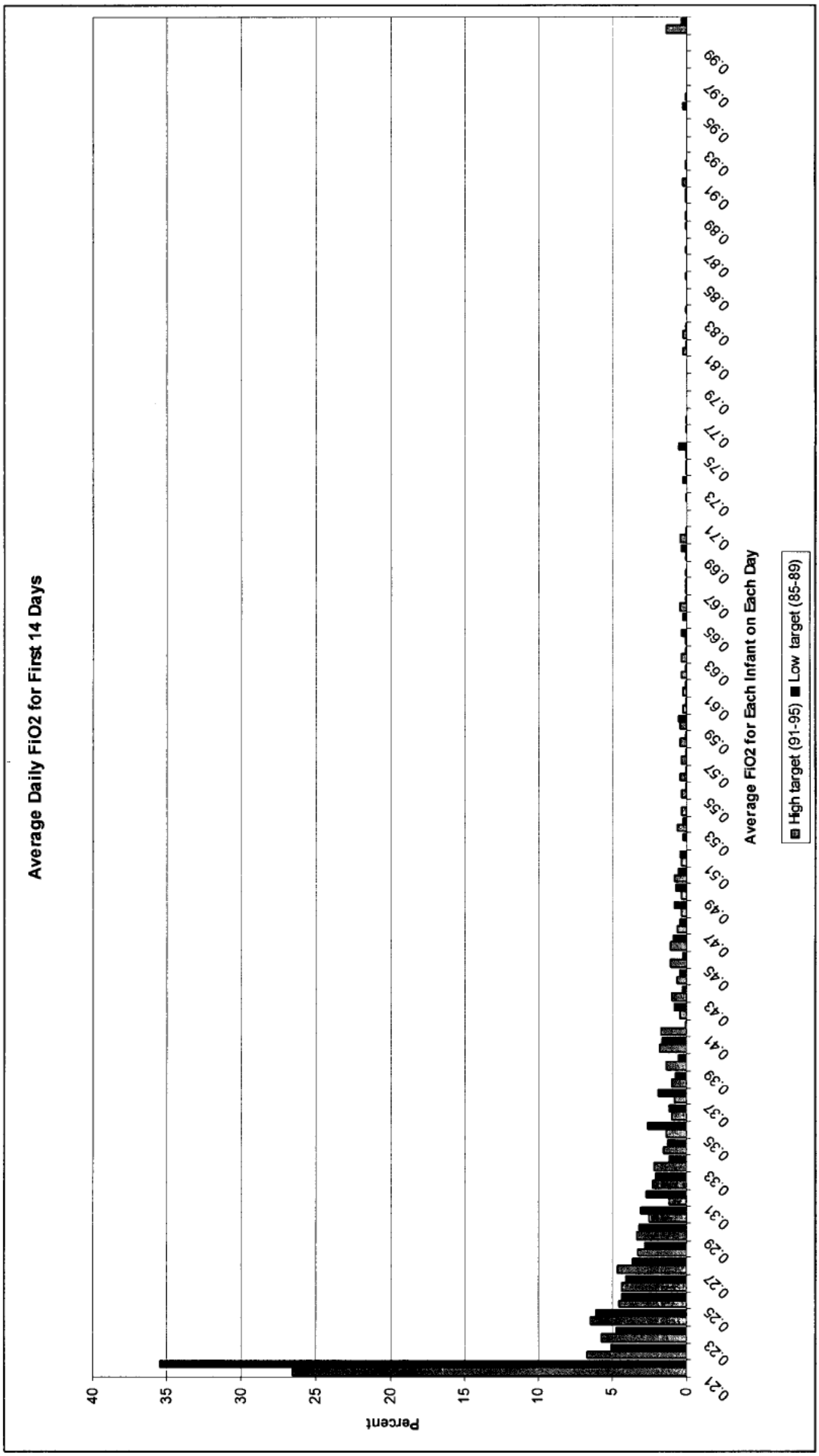
Summary statistics

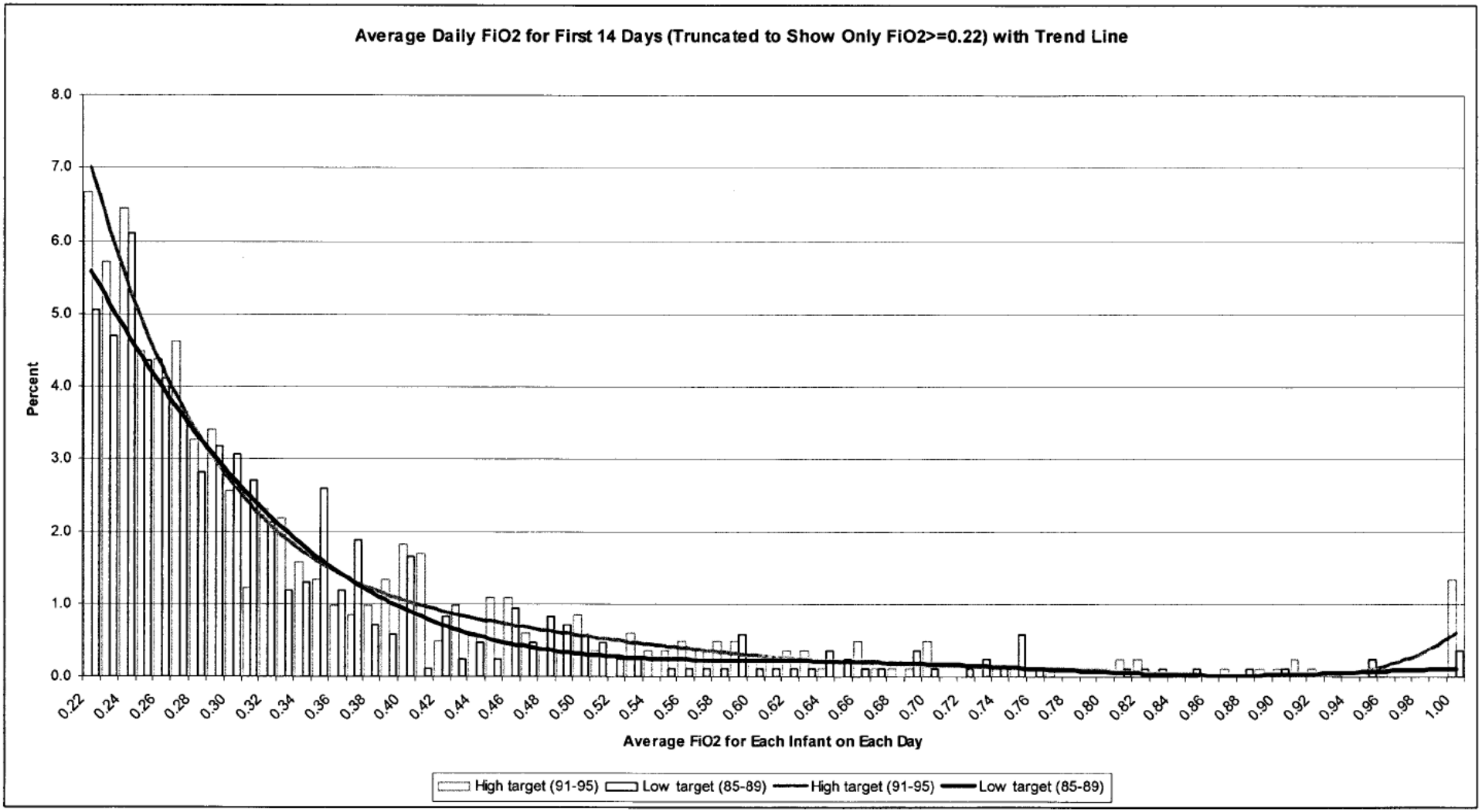
FiO2	High target (91-95)	Low target (85-89)
Mean	0.315	0.294
Maximum	1.000	1.000
90th percentile	0.500	0.447
75th percentile	0.466	0.317
Median	0.260	0.247
25th percentile	0.213	0.210
10th percentile	0.210	0.210
Minimum	0.210	0.210

Full distribution

Daily average FiO2 (interval lower bound)	High target (91-95)		Low target (85-89)	
	Percent	Cumulative	Percent	Cumulative
0.21	26.6	26.6	35.5	35.5
0.22	6.7	33.3	5.1	40.5
0.23	5.7	39.0	4.7	45.2
0.24	6.4	45.4	6.1	51.4
0.25	4.5	49.9	4.3	55.7
0.26	4.4	54.2	4.1	59.8
0.27	4.6	58.9	3.6	63.5
0.28	3.3	62.1	2.8	66.3
0.29	3.4	65.5	3.2	69.4
0.30	2.5	68.1	3.1	72.5
0.31	1.2	69.3	2.7	75.2
0.32	2.3	71.6	2.1	77.3
0.33	2.2	73.8	1.2	78.5
0.34	1.6	75.4	1.3	79.8
0.35	1.3	76.7	2.6	82.4
0.36	1.0	77.7	1.2	83.5
0.37	0.8	78.5	1.9	85.4
0.38	1.0	79.5	0.7	86.1
0.39	1.3	80.8	0.6	86.7
0.40	1.8	82.6	1.6	88.4
0.41	1.7	84.3	0.1	88.5
0.42	0.5	84.8	0.8	89.3
0.43	1.0	85.8	0.2	89.5
0.44	0.6	86.4	0.5	90.0
0.45	1.1	87.5	0.2	90.2
0.46	1.1	88.6	0.9	91.2
0.47	0.6	89.2	0.5	91.7
0.48	0.4	89.6	0.8	92.5
0.49	0.4	89.9	0.7	93.2
0.50	0.8	90.8	0.6	93.8
0.51	0.4	91.1	0.5	94.2

0.52	0.0	91.1	0.2	94.5
0.53	0.6	91.7	0.2	94.7
0.54	0.4	92.1	0.0	94.7
0.55	0.4	92.5	0.1	94.8
0.56	0.5	93.0	0.1	94.9
0.57	0.4	93.3	0.1	95.1
0.58	0.5	93.8	0.1	95.2
0.59	0.5	94.3	0.6	95.8
0.60	0.2	94.5	0.1	95.9
0.61	0.2	94.8	0.1	96.0
0.62	0.4	95.1	0.1	96.1
0.63	0.4	95.5	0.1	96.2
0.64	0.1	95.6	0.4	96.6
0.65	0.0	95.6	0.2	96.8
0.66	0.5	96.1	0.1	96.9
0.67	0.1	96.2	0.1	97.1
0.68	0.1	96.4	0.0	97.1
0.69	0.1	96.5	0.4	97.4
0.70	0.5	97.0	0.1	97.5
0.71	0.0	97.0	0.0	97.5
0.72	0.0	97.0	0.1	97.6
0.73	0.0	97.0	0.2	97.9
0.74	0.1	97.1	0.1	98.0
0.75	0.1	97.2	0.6	98.6
0.76	0.0	97.2	0.1	98.7
0.77	0.1	97.3	0.0	98.7
0.78	0.0	97.3	0.0	98.7
0.79	0.0	97.3	0.0	98.7
0.80	0.0	97.3	0.0	98.7
0.81	0.2	97.6	0.1	98.8
0.82	0.2	97.8	0.1	98.9
0.83	0.0	97.8	0.1	99.1
0.84	0.0	97.8	0.0	99.1
0.85	0.0	97.8	0.1	99.2
0.86	0.0	97.8	0.0	99.2
0.87	0.1	97.9	0.0	99.2
0.88	0.0	97.9	0.1	99.3
0.89	0.1	98.1	0.0	99.3
0.90	0.1	98.2	0.1	99.4
0.91	0.2	98.4	0.0	99.4
0.92	0.1	98.5	0.0	99.4
0.93	0.0	98.5	0.0	99.4
0.94	0.0	98.5	0.0	99.4
0.95	0.0	98.5	0.2	99.6
0.96	0.1	98.7	0.0	99.6
0.97	0.0	98.7	0.0	99.6
0.98	0.0	98.7	0.0	99.6
0.99	0.0	98.7	0.0	99.6
1.00	1.3	100.0	0.4	100.0





Daily FiO2 values for first 14 days of life (FiO2>=0.22 only)
Average daily FiO2 for each infant (average of 3 FiO2 measurements on SUPP05)
Includes data on 148 infants (71 High target, 77 Low target) for whom pulse oximeter data is available
12-5-05

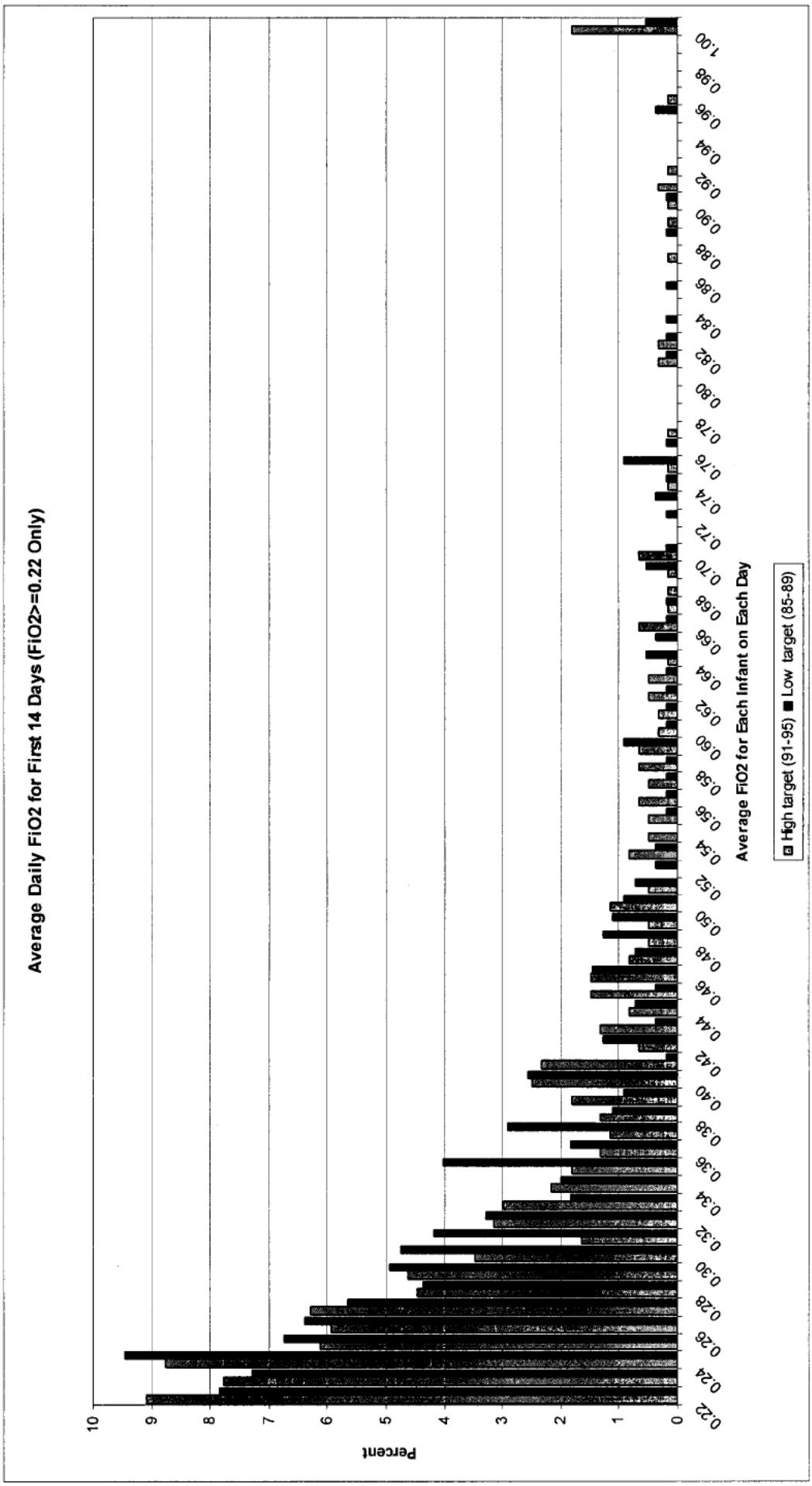
Summary statistics

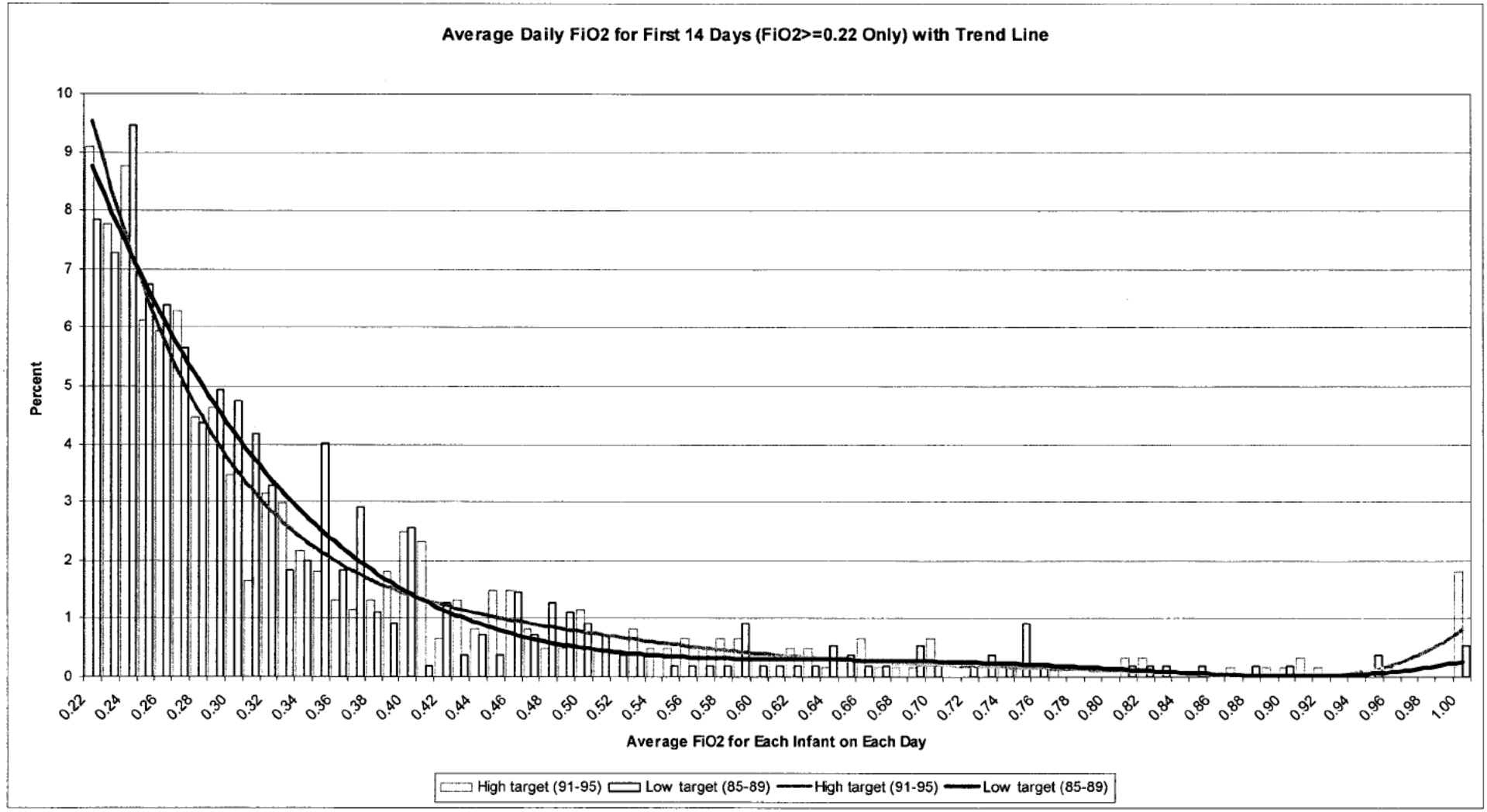
FiO2	High target (91-95)	Low target (85-89)
Mean	0.353	0.340
Maximum	1.000	1.000
90th percentile	0.563	0.503
75th percentile	0.400	0.370
Median	0.290	0.293
25th percentile	0.246	0.250
10th percentile	0.230	0.230
Minimum	0.220	0.220

Full distribution

FiO2	High target (91-95)		Low target (85-89)	
(interval lower bound)	Percent	Cumulative	Percent	Cumulative
0.22	9.09	9.1	7.83	7.8
0.23	7.77	16.9	7.29	15.1
0.24	8.76	25.6	9.47	24.6
0.25	6.12	31.7	6.74	31.3
0.26	5.95	37.7	6.38	37.7
0.27	6.28	44.0	5.65	43.4
0.28	4.46	48.4	4.37	47.7
0.29	4.63	53.1	4.92	52.6
0.30	3.47	56.5	4.74	57.4
0.31	1.65	58.2	4.19	61.6
0.32	3.14	61.3	3.28	64.8
0.33	2.98	64.3	1.82	66.7
0.34	2.15	66.4	2.00	68.7
0.35	1.82	68.3	4.01	72.7
0.36	1.32	69.6	1.82	74.5
0.37	1.16	70.7	2.91	77.4
0.38	1.32	72.1	1.09	78.5
0.39	1.82	73.9	0.91	79.4
0.40	2.48	76.4	2.55	82.0
0.41	2.31	78.7	0.18	82.1
0.42	0.66	79.3	1.28	83.4
0.43	1.32	80.7	0.36	83.8
0.44	0.83	81.5	0.73	84.5
0.45	1.49	83.0	0.36	84.9
0.46	1.49	84.5	1.46	86.3
0.47	0.83	85.3	0.73	87.1
0.48	0.50	85.8	1.28	88.3
0.49	0.50	86.3	1.09	89.4
0.50	1.16	87.4	0.91	90.3
0.51	0.50	87.9	0.73	91.1
0.52	0.00	87.9	0.36	91.4
0.53	0.83	88.8	0.36	91.8
0.54	0.50	89.3	0.00	91.8

0.55	0.50	89.8	0.18	92.0
0.56	0.66	90.4	0.18	92.2
0.57	0.50	90.9	0.18	92.3
0.58	0.66	91.6	0.18	92.5
0.59	0.66	92.2	0.91	93.4
0.60	0.33	92.6	0.18	93.6
0.61	0.33	92.9	0.18	93.8
0.62	0.50	93.4	0.18	94.0
0.63	0.50	93.9	0.18	94.2
0.64	0.17	94.0	0.55	94.7
0.65	0.00	94.0	0.36	95.1
0.66	0.66	94.7	0.18	95.3
0.67	0.17	94.9	0.18	95.4
0.68	0.17	95.0	0.00	95.4
0.69	0.17	95.2	0.55	96.0
0.70	0.66	95.9	0.18	96.2
0.71	0.00	95.9	0.00	96.2
0.72	0.00	95.9	0.18	96.4
0.73	0.00	95.9	0.36	96.7
0.74	0.17	96.0	0.18	96.9
0.75	0.17	96.2	0.91	97.8
0.76	0.00	96.2	0.18	98.0
0.77	0.17	96.4	0.00	98.0
0.78	0.00	96.4	0.00	98.0
0.79	0.00	96.4	0.00	98.0
0.80	0.00	96.4	0.00	98.0
0.81	0.33	96.7	0.18	98.2
0.82	0.33	97.0	0.18	98.4
0.83	0.00	97.0	0.18	98.5
0.84	0.00	97.0	0.00	98.5
0.85	0.00	97.0	0.18	98.7
0.86	0.00	97.0	0.00	98.7
0.87	0.17	97.2	0.00	98.7
0.88	0.00	97.2	0.18	98.9
0.89	0.17	97.4	0.00	98.9
0.90	0.17	97.5	0.18	99.1
0.91	0.33	97.9	0.00	99.1
0.92	0.17	98.0	0.00	99.1
0.93	0.00	98.0	0.00	99.1
0.94	0.00	98.0	0.00	99.1
0.95	0.00	98.0	0.36	99.5
0.96	0.17	98.2	0.00	99.5
0.97	0.00	98.2	0.00	99.5
0.98	0.00	98.2	0.00	99.5
0.99	0.00	98.2	0.00	99.5
1.00	1.82	100.0	0.55	100.0





From: Barbara Stoll
To: nfiner@ucsd.edu
Cc: Augusto Sola; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Valuable information from the data from SUPPORT
Date: Sunday, December 11, 2005 12:09:52 PM

Thanks Neil
I would not consider giving less than RA to anyone at this point-- without
a lot of convincing data!!!!
BJS<nfiner@ucsd.edu> writes:
>Hi Augusto and Barbara
>I appreciate your review of the data to date. I agree with many of the
>points raised by Augusto.
>We have used the medians in our response to the DSMC as suggested and they
>are different between the groups: 94% vs 92% and lower than the medians
>described by Hagadorn.
>In addition the groups also differ by the time in room air which is 10%
>greater for the lower range infants (85-89%)
>A most recent analyses also shows that the infants in room air spend more
>time at SpO2 values of 98% 99% and 100% than do the infants in oxygen in
>either group. Thus if SpO2 itself is toxic we would need to consider a new
>approach to the ELBW infant, ie giving nitrogen etc to keep the SpO2
>lower.
>The other side is that the oxygen being delivered is toxic apart from the
>FiO2. This is all new data not previously known, so we are learning from
>the
>trial to date.
>Thanks for your thoughts
>Neil
>
>
>-----Original Message-----
>From: Barbara Stoll [mailto:barbara.stoll@oz.ped.emory.edu]
>Sent: Friday, December 09, 2005 10:29 AM
>To: nfiner@ucsd.edu
>Subject: Fwd: Valuable information from the data from SUPPORT
>
>
>Hello
>I just sent comments below to Dr Stoll, and realized I did not cc you.
>Thanks
>Augusto
>
>----- Original Message -----
>
> Thursday, December 08, 2005 9:51:18 PM
>Message
>From: Augusto Sola
>Subject: Valuable information from the data from SUPPORT
>To: Barbara Stoll
>
>Barbara
>I have reviewed the data as sent by you.
>If you so decide, I give my consent for you to share with PI and/or others
>my assessment of the data as submitted, that I evaluated and believe

>contains important clinical information.
>
>Total numbers of hours analyzed: > 100,000
>153 infants.
>
>1) Saturation > 95% (High risk for hyperoxia): More than 2 times more risk
>in high treatment group.
> 36.2% of the time in high treatment group vs 14.9% of the time in low
>treatment group. This suggests that "choosing a higher target" exposes
>infants to undesired higher risk of hyperoxemia. This is clinically very
>important from safety concern regarding increased exposure to periods of
>undesired hyperoxemia.
>Even though I do not have all the raw data in hours to do a detailed
>analysis, this information of 36.2% vs 14.9% shows in simple analysis a
>significant risk reduction to avoid periods of hyperoxemia by using lower
>O2 Sat Targets.
>
>2) Time with Saturation levels 85-95%:
>In the low treatment group, 66.2% of the time the Saturation is 85-95%
>In the High treatment group this only occurs 55.2% of the time.
>(Based on number of hours, this difference is also very likely to be
>highly significant).
>If this were "an accepted range", the information lends support to the
>fact that
>
>3) Time below "respective" target:
>High Treatment group: 24.3% of the time below target of 91-95% Sat level;
>and 8.6% of the time below 85% Sat level.
>Low treatment group: 18.9% of the time below 85% Sat level (or below
>target of 85-89% sat)
>
>4) "Mean" O2 sat levels: I believe that using "mean" O2 levels (as shown
>is the last column to the right) it may be an incorrect way of analyzing
>the data from this study to convert it into valuable information.
>These are not normal distributions. (Median, extreme values, etc may be
>better).
>90% mean sat level in low treatment group and 92.2% mean sat level in high
>treatment group may be significant, but clinically that may have no value
>at all.
>
>If the information that can be derived from the data you sent us is
>correct, then I believe the following are important:
>a) There in fact appears to be a "substantial separation" between the
>groups.
>b) If intention to treat and risks of hyperoxemia and hypoxemia are
>considered, the groups are different (as shown above in 1) in regards to
>the time of exposure to high risk of hyperoxemia. This is important
>information to share as is with clinicians.
>Furthermore, if a Sat level less than 85% is undesirable, then 18.9% vs
>8.6% of the time may be unacceptable. However, < 85% may e 83 and 84% or
>70-75%. I would suggest evaluating in detail the time spent between
>different sat levels at low end (i.e.: 82-85% , 80-82%, 75-80% and less
>than 75% in both groups and compare.)
>
>In addition to the above, there may be even more important clinical
>effects that could become known by completing the study.
>

>Thank you
>
>Augusto Sola
>
>
>
>
>

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
Medical Director, Children's Healthcare of Atlanta at Egleston
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD) [E]
Cc:	"Neil Finer"; "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Maynard Rasmussen"; "Michele"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Subject:	RE:
Date:	Friday, December 09, 2005 8:30:15 PM
Attachments:	SUPPORT Trial DSMC Response.ppt Percent of time spent at each SpO2 value (FiO2 gt21) 12-5-05.doc Pct of time at all O2 values (room air only) 12-9-05.xls

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Hi Rose and Everyone
I have spoken to Barbara and had email exchanges with Augusto.
My main issue at present is to have a clear presentation to the DSMC. I asked Marie to run some additional analyses. She also ran the data for only those days that the infants were in oxygen at all 3 time points as this is the best data to trim out the room air contamination.
The actual data is increasingly beneficial as it shows less real time > 95%, and maintains the groups separation. It also shows that 91% to 95% group in narrow target for about 55% of the time with 85% to 89% being in target about 25% of the time. I think lowering the high alarm to 94% will increase this time in target in booth groups.
I would like to use the PowerPoint for the DSMC
What do you think?
I have attached the newer analyses
Thanks for reviewing this
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 09, 2005 11:43 AM
To: nfiner@ucsd.edu
Subject:

Neil
I spoke to Barbara regarding the recent email communication you had forwarded to me. She will likely call you.
We will develop language to post on either our public website or the clinicaltrials.gov website to inform folks of the trial pending the dsmc meeting and director recommendations next week for uniformity.
Thanks for you help and candor!
Rose

Sent from my BlackBerry Wireless Handheld

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

December 9 2005

Report of the DSMC Nov 2005

The DSMC expressed 2 concerns:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

Report of the DSMC Nov 2005

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Evidence for Current SpO2 Ranges

- No current prospective studies that have evaluated actual durations of time at various SpO2 levels
- Median SpO2 in healthy preterm infants = 97% (Ng et al Arch Dis Child 1998;79:F64)
- All published studies reported target ranges ie lower vs higher using High SpO2 limits -92% vs 95%) for populations but did not present any data as to how well these target were adhered to.
- Sun et al compared units with upper limits of >95% with those of $\leq$ 95% (Ped Res 2002, 51:350A)

Evidence for Current SpO2 Ranges

- **To maintain PaO2 between 40 and 90mmHg would require SpO2 alarms of 92.5% to 95% (Paky et al Acta Paediatr. 1995 Jun; 84(6):613-6.)**

Evidence for Current SpO2 Ranges

- **Tin et al reported units by the limits they set without any individual patient data (Tin et al Arch Dis Child 2001;84:F106)**
- **Another survey compared SpO2 limits > 98% with ≤ 98%, and early limits – first 2 weeks- of > 92% vs < 92% (Anderson Ped Res 2002;51:367A)**
- **Chow et al reported on a change of practice with lowering of the SPo2 limit and other changes – They did not provide any actual SpO2 data (Chow et al, Pediatr 2003;111:339)**
- **All of these studies suggested that lower SpO2 limits were associated with less ROP.**

Evidence for Current SpO2 Ranges

- **Prior to the initiation of SUPPORT – there were no data indicating the actual percent of time ELBW infants spend at different SpO2 values or ranges**
- **The design of the trial using oximeter downloads was unique and will provide this information based on a large prospective cohort**
- **This trial was also unique in collecting this data from 2 hours of age in acutely unstable ELBW infants until there are out of oxygen**

Response to DSMC

Safety Issue of SpO2>95%

Concern regarding safety issue of duration of SpO2 > 95%

- ✓ **The current best data from Hagadorn et al evaluated 78 ELBW infants for 70 hours per week for the first 4 weeks of life**
- ✓ **Lower and upper limits were 83% -92% and 92%-98%**
- ✓ **Median SpO2 = 95%**
- ✓ **Medians from SUPPORT Oximeter groups – 92% and 94%, and for infants only in oxygen for the entire day the medians are 91% vs 93%.**

Response to DSMC:
Safety Issue of SpO2>95%

- STOP-ROP high treatment infants spent 97% of time > 95%
- Case Western a current NRN Center – Current data from SUPPORT type ELBW infants – SpO2 > 95% for > 50% time
- SUPPPORT Infants on room air – SpO2 > 95% from 46% to 69% of time

Response to DSMC:
Safety Issue of SpO2>95%

- **Additional analyses evaluated the duration of time at SpO2 values of 98%, 99% and 100% as these may represent very high PaO2 values**
- **Infants in SUPPORT in ROOM Air spend more time at these values than infants receiving oxygen – 32% - 38% versus 5%-6%**

SUPPORT Trial Actual Results

91% - 95% Room Air 85% - 89%

98%	15.49%	77.15	13.65%	81.42
99%	12.94%	90.09	10.37%	91.79
100%%	9.91%	100.00	8.21%	100.00
Total	**38.3%**		**32.2%**	

91% - 95% Oxygen 85% - 89%

98%	3.51%	96.90	2.66%	97.23
99%	1.90%	98.80	1.60%	98.83
100%	1.20%	100.00	1.17%	100.00
Total	**6.6%**		**5.4%**	

Response to DSMC: Safety Issue of SpO2>95%

- The actual algorithm for conversion of displayed versus actual values results in inability to create a whole value for each displayed value.
- We calculated the time that infants were > 96%

  and < 84%
- These values may be the first such data for a large group of ELBW infants that has been reported.
- These values appear lower than any previous reports

Response to DSMC: Safety Issue of SpO2>95%

Percent of time of spent at SpO2 < 84% and > 96% (RTI Analyses In Oxygen, Dec 2, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.30%	14.05%
> 96%	21.45%	15.47%

Response to DSMC: Safety Issue of SpO2>95%

- **We believe that neither oximeter group in the SUPPORT trial is being exposed to excessive durations of SpO2 > 95% based on all currently available information and the actual SUPPORT Trial Data analyzed to date.**
- **Current analyses demonstrate that the highest duration of SpO2 > 95% was 28.13%, the lowest value that we believe has been reported for any group of preterm infants. In addition for some of the time in this analyses, infants were receiving room air, which increases SpO2 values > 96%**

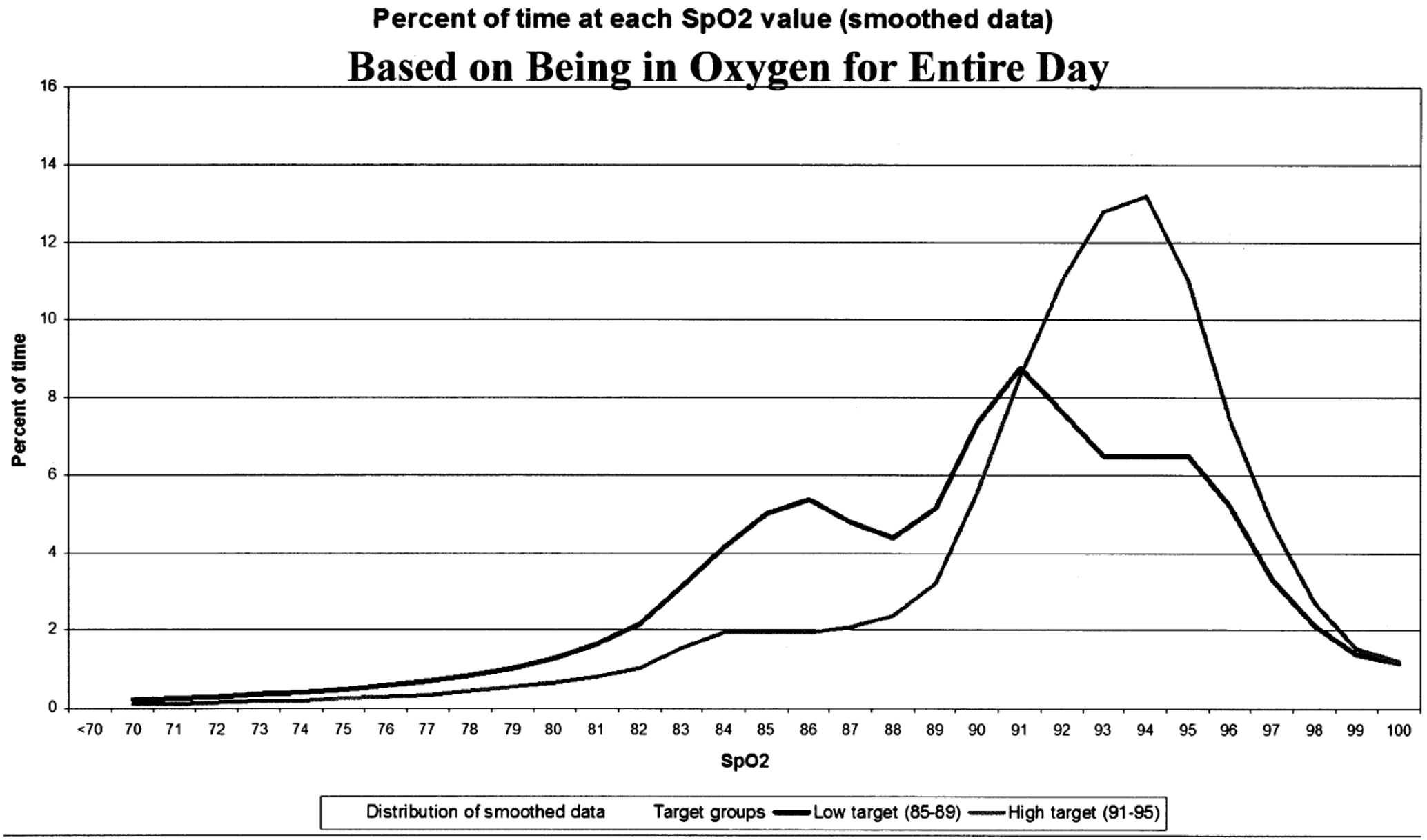
Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **Further analyses which included only infants on Oxygen at all 3 data points for a given day revealed even less duration of SpO2 > 96% - 20.2% vs9.39%**
- **This analyses avoids the contamination of room air time with resultant higher SpO2 values**

Range Assigned	Data for days in Oxygen – all 3 data points > .21 High target (91-95)	Low target (85-89)
< 84%	6.40%	13.3%
≥ 96%	20.2%	9.39%

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **An evaluation of the oximeter group data has revealed that there is a difference in the mean - 90% vs 92% and median values for the 2 groups – 92% vs 94%**
- **The Median SpO2s obtained using only days that were in oxygen at all 3 data points were 91% vs 93%**
- **These additional analyses have demonstrated that the cumulative time spent with an SpO2 of 90% or less is 22.8.0% (91% - 95%) versus 47.6% (85% - 89%) for a > 20% absolute difference between the groups.**



Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **The time in actual Target using only days when infants are in oxygen for all 3 data points**

91-95% = 55% 85% - 89% = 24.6%

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **It is uncertain what duration of differences will be associated with different short and long term outcomes, but we are achieving some separation to the present.**
- **We believe that greater separation is possible and have made a number of recommendations to ensure that this will occur**

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **The 91% - 95% are more in target because their alarm sounds when they reach 95%**

✘ **The 85% - 89% are less time in target because when their SpO2 is > 89% (a reading of 93%) there is no alarm. The alarm only sounds at a reading of 95%**

✓ **We believe that we can improve this time in range by lowering the high alarm to 94%**

Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups

1. **Set high SpO2 limit – alarm to 94%. This will reduce the duration of SpO2 values > 95% for both groups, and should increase the time both groups spend in the narrow target range.**
2. **Require documentation that the oximeters alarm limits are set and functional as per protocol every 4-6 hours**
3. **Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect saturations measured while on oxygen therapy and exclude saturations of infants in room air**

Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups

4. Further training and in-service at all the sites to stress the importance of keeping the SpO2 alarms functional and at the limits of 85% and 95%. We will use the OWL (Oxygen with Love Program) developed at Oschner.
5. Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation
6. Place bedside cards to indicate the desired target range

Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups

7. **Initiate compliance monitoring visits coordinated by RTI to visit random sites**
8. **Reanalyze group differences after an additional 100-150 infants have been enrolled.**

Percent of time spent at each SpO2 value for infants with FiO2 > 0.21 at each of three timepoints recorded on SUPP05

Data processed as of 12/02/2005

Data included in tables and graphs

Infants included	High target (91-95)	Low target (85-89)	Total
Number	65	62	127
Hours	8703	7513	16216

Percent of time spent at each actual SpO2 value, by treatment group

	High target (91-95)		Low target (85-89)	
SpO2	Percent	Cumulative	Percent	Cumulative
<70	0.73	0.73	1.75	1.75
70	0.09	0.82	0.21	1.96
71	0.11	0.93	0.24	2.20
72	0.12	1.06	0.27	2.48
73	0.15	1.21	0.33	2.80
74	0.18	1.39	0.38	3.19
75	0.22	1.60	0.44	3.63
76	0.26	1.86	0.53	4.16
77	0.31	2.17	0.62	4.78
78	0.38	2.55	0.75	5.53
79	0.49	3.04	0.93	6.46
80	0.61	3.65	1.14	7.60
81	0.73	4.38	1.45	9.05
82	0.90	5.28	1.86	10.91
83	1.12	6.39	2.42	13.34
84	0.00	6.39	2.30	15.64
84.25	0.00	6.39	0.95	16.59
84.5	0.00	6.39	1.04	17.63
84.75	0.00	6.39	1.15	18.78
85	0.00	6.39	2.83	21.61
85.5	7.79	14.19	0.00	21.61
86	0.00	14.19	5.54	27.14
87	0.00	14.19	5.21	32.36
88	2.22	16.40	4.37	36.72
89	2.50	18.90	4.38	41.11
90	3.90	22.80	5.95	47.06
91	7.20	30.00	8.72	55.78
92	9.90	39.90	8.79	64.56
93	12.17	52.07	0.00	64.56
94	13.37	65.44	0.00	64.56
94.5	0.00	65.44	26.05	90.61
95	8.58	74.02	0.00	90.61
95.25	3.09	77.11	0.00	90.61
95.5	2.72	79.82	0.00	90.61
95.75	2.51	82.33	0.00	90.61
96	5.10	87.44	0.00	90.61
97	5.96	93.39	3.96	94.56
98	3.51	96.90	2.66	97.23
99	1.90	98.80	1.60	98.83
100	1.20	100.00	1.17	100.00

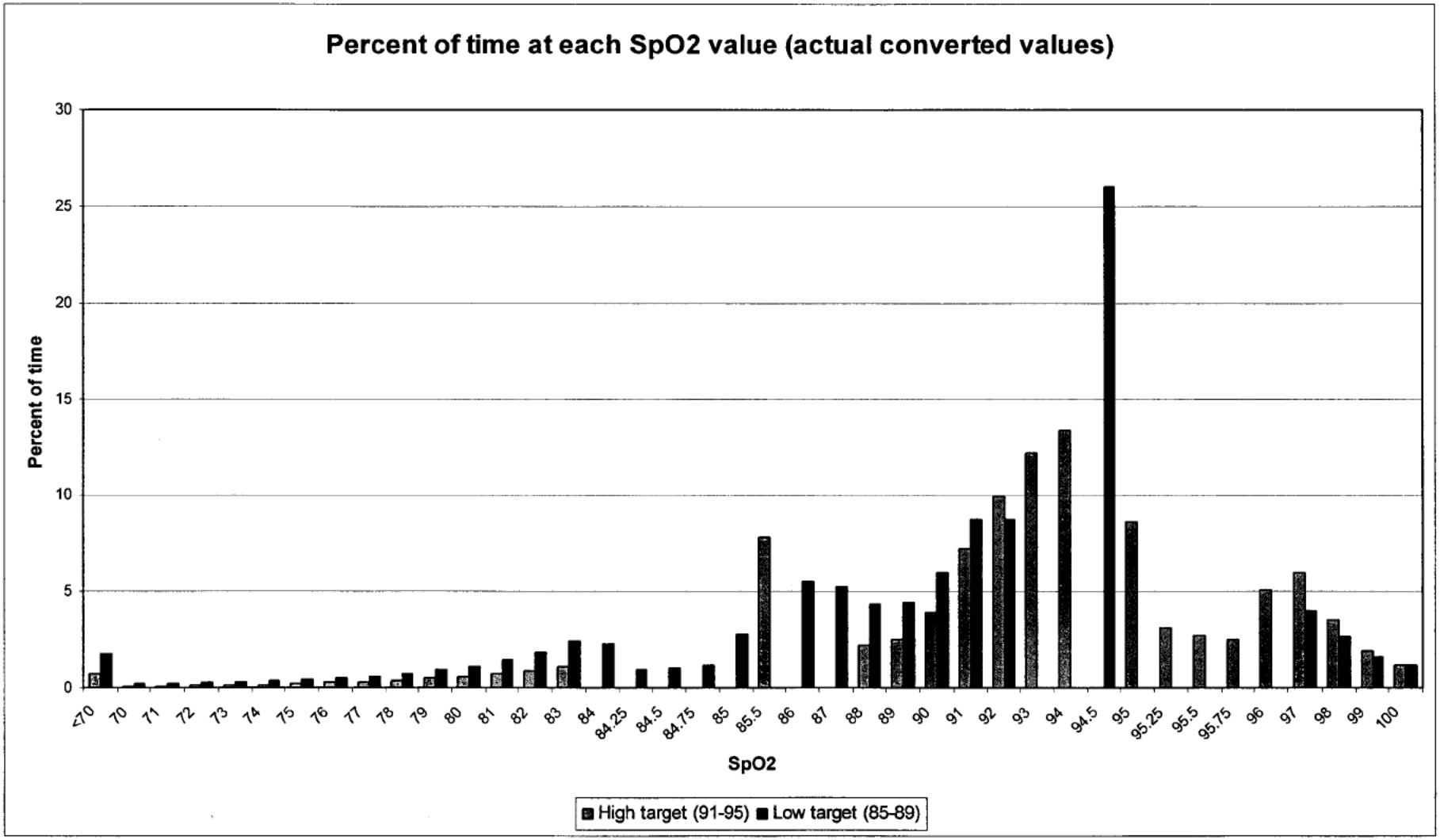
Median SpO2

	High target (91-95)	Low target (85-89)
Median	93	91

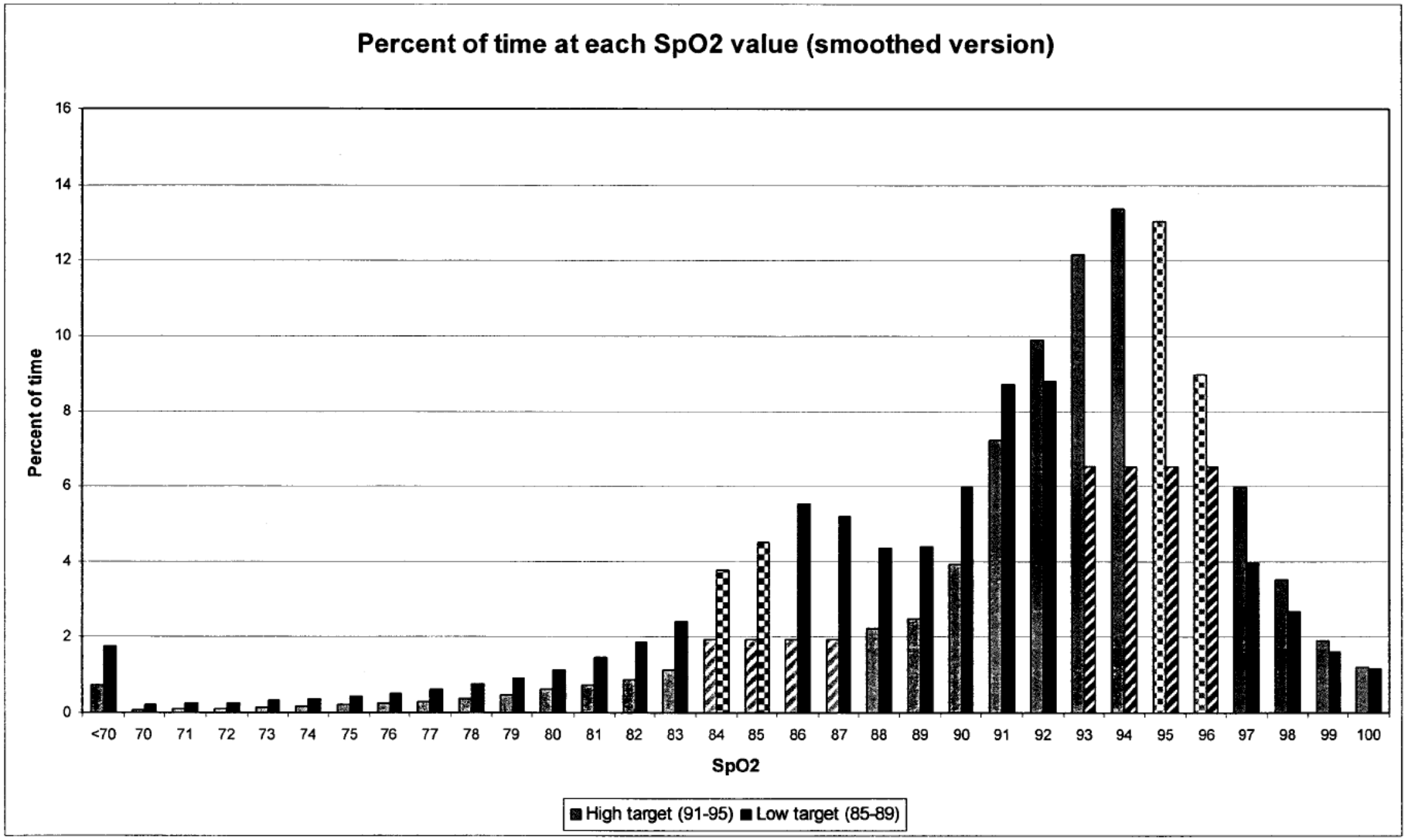
Percent of time of spent at SpO2 <84 and >96

Range	High target (91-95)	Low target (85-89)
<84	6.39	13.34
>96	12.56	9.39

The graph below displays each individual converted SpO2 value



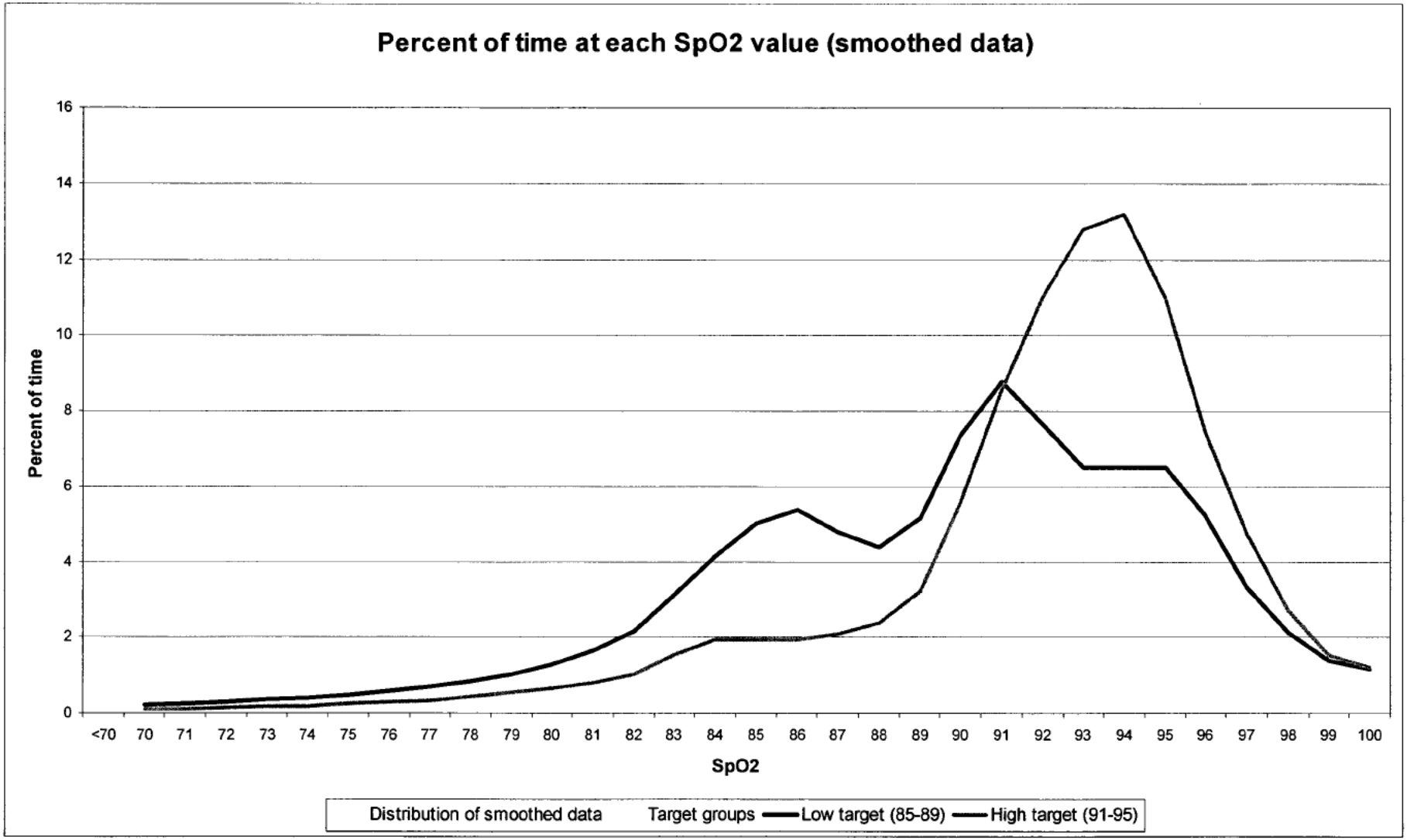
In the graph below, the converted SpO2 values have been smoothed to give a better idea of the distribution. Adjustments made to smooth the data are listed on the following page. Patterns are used to identify altered values.



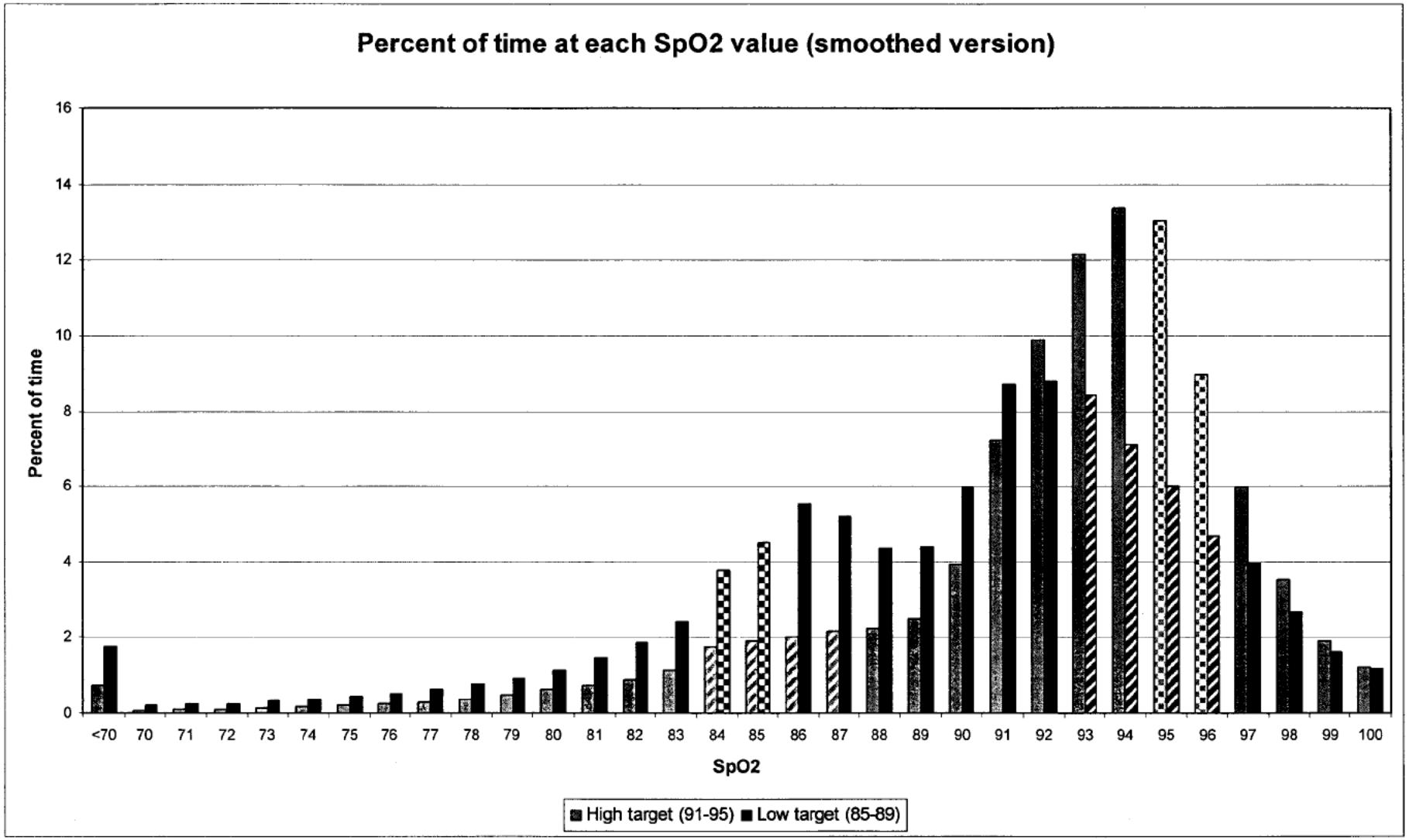
Changes made to achieve smoothing

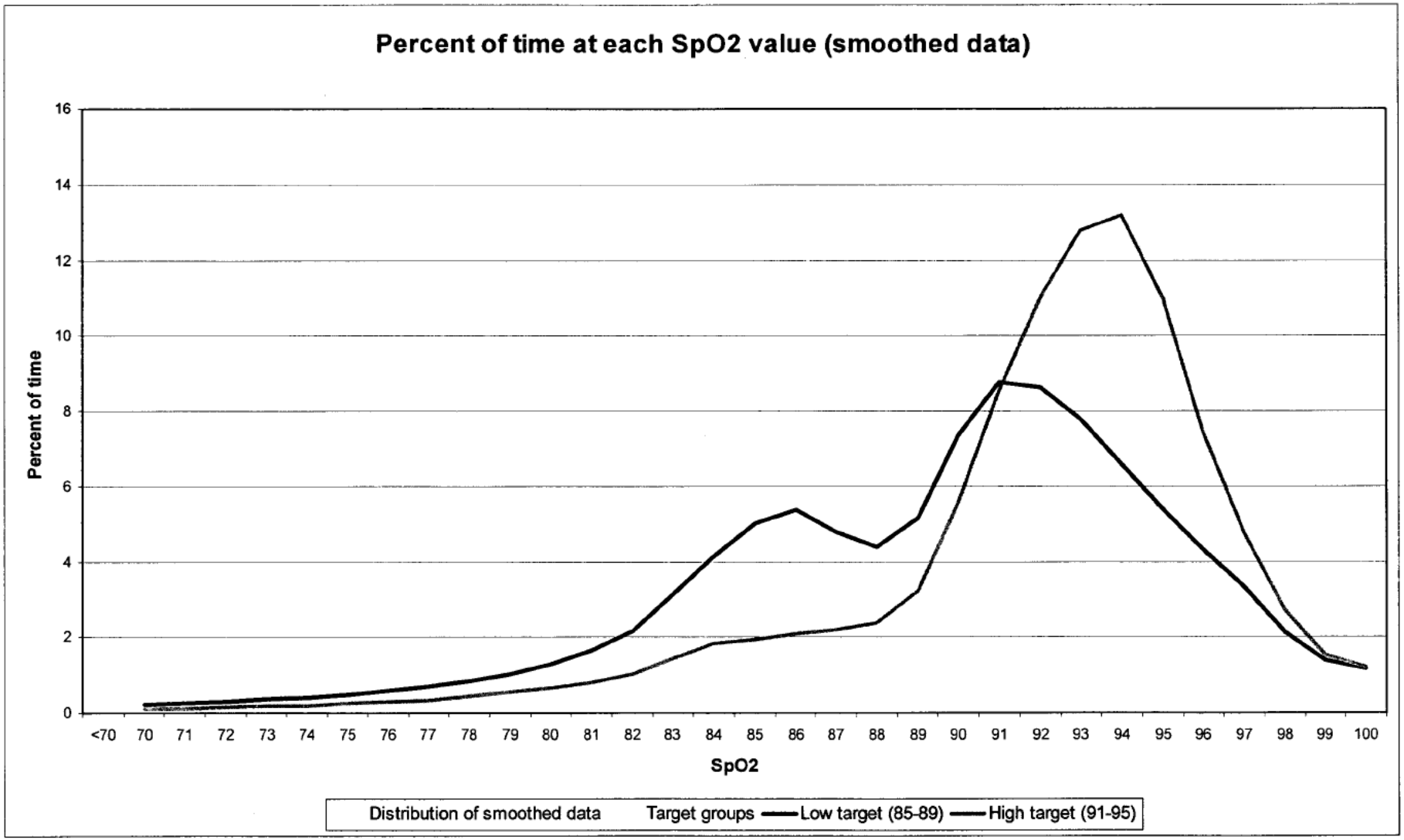
High target (91-95)	Pattern
Percent of time at converted value of 85.5 are spread evenly over 84-87	Blue diagonal stripes
Percent of time at 95 includes converted values of 95, 95.25 and half the percent of time at 95.5	Blue checked
Percent of time at 96 includes converted values of 96, 95.75 and half the percent of time at 95.5	Blue checked

Low target (85-89)	Pattern
Percent of time at converted value of 94.5 are spread evenly over 93-96	Burgundy diagonal stripes
Percent of time at 84 includes converted values of 84, 84.25 and half the percent of time at 84.5	Burgundy checked
Percent of time at 85 includes converted values of 85, 84.75 and half the percent of time at 84.5	Burgundy checked



The following two graphs are the result of some additional smoothing.





Percent of time spent in each ACTUAL SpO2 range
Days on room air only

	High target (91-95)		Low target (85-89)	
SpO2	Percent	Cumulative	Percent	Cumulative
<70	0.42	0.42	0.40	0.40
70	0.05	0.47	0.05	0.46
71	0.06	0.53	0.06	0.52
72	0.07	0.60	0.07	0.59
73	0.08	0.68	0.08	0.67
74	0.09	0.77	0.10	0.77
75	0.11	0.88	0.12	0.89
76	0.13	1.01	0.14	1.03
77	0.15	1.15	0.17	1.20
78	0.17	1.32	0.21	1.41
79	0.20	1.52	0.25	1.66
80	0.24	1.77	0.30	1.96
81	0.29	2.06	0.38	2.34
82	0.34	2.40	0.46	2.80
83	0.41	2.82	0.59	3.38
84	0.00	2.82	0.47	3.86
84.25	0.00	2.82	0.20	4.06
84.5	0.00	2.82	0.21	4.27
84.75	0.00	2.82	0.22	4.49
85	0.00	2.82	0.57	5.06
85.5	2.53	5.35	0.00	5.06
86	0.00	5.35	1.14	6.21
87	0.00	5.35	1.19	7.40
88	0.92	6.26	1.22	8.62
89	1.11	7.37	1.43	10.05
90	1.49	8.85	2.03	12.09
91	2.27	11.12	3.23	15.32
92	3.35	14.47	4.44	19.76
93	4.76	19.22	0.00	19.76
94	6.73	25.95	0.00	19.76
94.5	0.00	25.95	34.20	53.95
95	5.82	31.77	0.00	53.95
95.25	2.58	34.36	0.00	53.95
95.5	2.68	37.03	0.00	53.95
95.75	2.86	39.89	0.00	53.95
96	7.39	47.28	0.00	53.95
97	14.38	61.66	13.82	67.78
98	15.49	77.15	13.65	81.42
99	12.94	90.09	10.37	91.79
100	9.91	100.00	8.21	100.00

From: Augusto Sola
To: nfiner@ucsd.edu
Cc: Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Valuable information from the data from SUPPORT
Date: Friday, December 09, 2005 3:21:29 PM

Thanks Neil
I'd have to disagree with some of the concepts in Room Air.
Sat 98-100% in Room air could be fairly well predict PaO2. The PaO2 in room air with those saturations will never be "low" nor "high". i.e.: PaO2 of (50) 55 mmHg at low end to 65-(75) mmHg at high end. So "hyperoxemia" is not possible.
Different could be the case with those sat levels when breathing supplemental oxygen. As you know sat monitors cannot detect hyperoxemia, and is impossible to predict PaO2 form those sat levels (sat is) and infant is breathing FiO2 > 21%.
I think that to avoid hyperoxemia and ("see-saw"; i.e wide variations) is not to be interpreted as permitting or inducing hypoxemia.
I would not consider giving a healthy preemie less than 21% Oxygen to breath. As described by Rigatto, Alvaro and others hypoxic gas leads to hypoventilation and more apnea (possibly then leading to giving supplemental O2 in clinical practice and/or to "up and down" and wide variations).
Thank you
Regards
Augusto

<nfiner@ucsd.edu> on Friday, December 09, 2005 at 1:55 PM +0000 wrote:
>Hi Augusto and Barbara
>I appreciate your review of the data to date. I agree with many of the
>points raised by Augusto.
>We have used the medians in our response to the DSMC as suggested and they
>are different between the groups: 94% vs 92% and lower than the medians
>described by Hagadorn.
>In addition the groups also differ by the time in room air which is 10%
>greater for the lower range infants (85-89%)
>A most recent analyses also shows that the infants in room air spend more
>time at SpO2 values of 98% 99% and 100% than do the infants in oxygen in
>either group. Thus if SpO2 itself is toxic we would need to consider a new
>approach to the ELBW infant, ie giving nitrogen etc to keep the SpO2
>lower.
>The other side is that the oxygen being delivered is toxic apart from the
>FiO2. This is all new data not previously known, so we are learning from
>the
>trial to date.
>Thanks for your thoughts
>Neil
>
>
>-----Original Message-----
>From: Barbara Stoll [mailto:barbara.stoll@oz.ped.emory.edu]
>Sent: Friday, December 09, 2005 10:29 AM
>To: nfiner@ucsd.edu

>Subject: Fwd: Valuable information from the data from SUPPORT
>
>
>Hello
>I just sent comments below to Dr Stoll, and realized I did not cc you.
>Thanks
>Augusto
>
>----- Original Message -----
>
> Thursday, December 08, 2005 9:51:18 PM
>Message
>From: Augusto Sola
>Subject: Valuable information from the data from SUPPORT
>To: Barbara Stoll
>
>Barbara
>I have reviewed the data as sent by you.
>If you so decide, I give my consent for you to share with PI and/or others
>my assessment of the data as submitted, that I evaluated and believe
>contains important clinical information.
>
>Total numbers of hours analyzed: > 100,000
>153 infants.
>
>1) Saturation > 95% (High risk for hyperoxia): More than 2 times more risk
>in high treatment group.
> 36.2% of the time in high treatment group vs 14.9% of the time in low
>treatment group. This suggests that "choosing a higher target" exposes
>infants to undesired higher risk of hyperoxemia. This is clinically very
>important from safety concern regarding increased exposure to periods of
>undesired hyperoxemia.
>Even though I do not have all the raw data in hours to do a detailed
>analysis, this information of 36.2% vs 14.9% shows in simple analysis a
>significant risk reduction to avoid periods of hyperoxemia by using lower
>O2 Sat Targets.
>
>2) Time with Saturation levels 85-95%:
>In the low treatment group, 66.2% of the time the Saturation is 85-95%
>In the High treatment group this only occurs 55.2% of the time.
>(Based on number of hours, this difference is also very likely to be
>highly significant).
>If this were "an accepted range", the information lends support to the
>fact that
>
>3) Time below "respective" target:
>High Treatment group: 24.3% of the time below target of 91-95% Sat level;
>and 8.6% of the time below 85% Sat level.
>Low treatment group: 18.9% of the time below 85% Sat level (or below
>target of 85-89% sat)
>
>4) "Mean" O2 sat levels: I believe that using "mean" O2 levels (as shown
>is the last column to the right) it may be an incorrect way of analyzing
>the data from this study to convert it into valuable information.
>These are not normal distributions. (Median, extreme values, etc may be
>better).
>90% mean sat level in low treatment group and 92.2% mean sat level in high

>treatment group may be significant, but clinically that may have no value
>at all.
>
>If the information that can be derived from the data you sent us is
>correct, then I believe the following are important:
>a) There in fact appears to be a "substantial separation" between the
>groups.
>b) If intention to treat and risks of hyperoxemia and hypoxemia are
>considered, the groups are different (as shown above in 1) in regards to
>the time of exposure to high risk of hyperoxemia. This is important
>information to share as is with clinicians.
>Furthermore, if a Sat level less than 85% is undesirable, then 18.9% vs
>8.6% of the time may be unacceptable. However, < 85% may e 83 and 84% or
>70-75%. I would suggest evaluating in detail the time spent between
>different sat levels at low end (i.e.: 82-85% , 80-82%, 75-80% and less
>than 75% in both groups and compare.)
>
>In addition to the above, there may be even more important clinical
>effects that could become known by completing the study.
>
>Thank you
>
>Augusto Sola
>
>
>
>
>

From: Hastings, Betty J.
To: Hastings, Betty J.; ckr3+@pitt.edu; cgleason@u.washington.edu; gavery123@hotmail.com; D'Alton, Mary (NIH/NICHD); Willinger, Marian (NIH/NICHD) [E]; Hunt, Carl (NIH/NHLBI) [E]; mcallen@jhmi.edu; merran.thomson@ic.ac.uk; rjb6j@hscmail.mcc.virginia.edu; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Berberich, Mary Anne (NIH/NHLBI) [E]
Cc: mck6@pitt.edu; milhil@u.washington.edu; poppoff@u.washington.edu; Simon, Malinda (NIH/NHLBI) [C]; Perez, Tania (NIH/NHLBI) [C]; zlv2102@columbia.edu
Subject: RE: SUPPORT Conference Call
Date: Friday, December 09, 2005 8:46:57 AM

Just a reminder of the conference call scheduled for Tuesday the 13th. Please let me know, by today, if you have not received the Fed-ex package with the material for this call. It was sent on the 6th and you should have received it on the 7th.

Thank you.
Betty

Dear DSMC Members,
The DSMC conference call, to discuss the SUPPORT study, has been scheduled for Tuesday, December 13, at 2:00pm EST. To join this call please **dial the toll free number 888-396(b) (6) and enter the numeric Passcode (b) (6) (# when prompted). (The USA Toll Number is +1-210-839-(b) (6).** The leader of the call is Dr. Abhik Das. The agenda, list of participants and material to be discussed will be sent by Fed-Ex on December 6th. Please let me know if you do **not** receive this material.

Thank you.
Betty

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 7709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
e-mail: bkh@rti.org

From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Augusto Sola
Subject: Fwd: Valuable information from the data from SUPPORT
Date: Thursday, December 08, 2005 10:00:59 PM

Rose
I sent Augusto an email about his comment-- I think he did not mean to write that is was stopped for "poor design"-- but rather that because it was stopped would be quite a while to have data that is of course important for clinical care practices.

He just sent me these comments. Please share
BJS

Barbara
I have reviewed the data as sent by you.
If you so decide, I give my consent for you to share with PI and/or others my assessment of the data as submitted, that I evaluated and believe contains important clinical information.

Total numbers of hours analyzed: > 100,000
153 infants.

1) Saturation > 95% (High risk for hyperoxia): More than 2 times more risk in high treatment group.
36.2% of the time in high treatment group vs 14.9% of the time in low treatment group. This suggests that "choosing a higher target" exposes infants to undesired higher risk of hyperoxemia. This is clinically very important from safety concern regarding increased exposure to periods of undesired hyperoxemia.
Even though I do not have all the raw data in hours to do a detailed analysis, this information of 36.2% vs 14.9% shows in simple analysis a significant risk reduction to avoid periods of hyperoxemia by using lower O2 Sat Targets.

2) Time with Saturation levels 85-95%:
In the low treatment group, 66.2% of the time the Saturation is 85-95%
In the High treatment group this only occurs 55.2% of the time.
(Based on number of hours, this difference is also very likely to be highly significant).
If this were "an accepted range", the information lends support to the fact that

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4) "Mean" O2 sat levels: I believe that using "mean" O2 levels (as shown is the last column to the right) it may be an incorrect way of analyzing the data from this study to convert it into valuable information.
These are not normal distributions. (Median, extreme values, etc may be better).

90% mean sat level in low treatment group and 92.2% mean sat level in high treatment group may be significant, but clinically that may have no value at all.

If the information that can be derived from the data you sent us is correct, then I believe the following are important:
a) There in fact appears to be a "substantial separation" between the groups.
b) If intention to treat and risks of hyperoxemia and hypoxemia are considered, the groups are different (as shown above in 1) in regards to the time of exposure to high risk of hyperoxemia. This is important information to share as is with clinicians.
Furthermore, if a Sat level less than 85% is undesirable, then 18.9% vs 8.6% of the time may be unacceptable. However, < 85% may e 83 and 84% or 70-75%. I would suggest evaluating in detail the time spent between different sat levels at low end (i.e.: 82-85% , 80-82%, 75-80% and less than 75% in both groups and compare.)

In addition to the above, there may be even more important clinical effects that could become known by completing the study.

Thank you

Augusto Sola

From: Hastings, Betty J.
To: Hastings, Betty J.; ckr3+@pitt.edu; cgleason@u.washington.edu; gavery123@hotmail.com; D'Alton, Mary (NIH/NICHD); Willinger, Marian (NIH/NICHD) [E]; Hunt, Carl (NIH/NHLBI) [E]; mcallen@jhmi.edu; merran.thomson@ic.ac.uk; rjb6j@hscmail.mcc.virginia.edu; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Berberich, Mary Anne (NIH/NHLBI) [E]
Cc: csd12@columbia.edu; mck6@pitt.edu; milhil@u.washington.edu; poppoff@u.washington.edu; Simon, Malinda (NIH/NHLBI) [C]; Perez, Tania (NIH/NHLBI) [C]
Subject: RE: SUPPORT Conference Call
Date: Wednesday, December 07, 2005 2:42:42 PM
Attachments: Daily FiO2 for first 14 days1.doc

I'm very sorry but I failed to send you the second part to the attached document. **Daily FiO2 values for first 14 days of life (FiO2>=0.22 only)**

Please use this version when reviewing the material for Tuesday's call.

<<Daily FiO2 for first 14 days1.doc>>
Thank you.
Betty

Dear DSMC Members,
The DSMC conference call, to discuss the SUPPORT study, has been scheduled for Tuesday, December 13, at 2:00pm EST. To join this call please **dial the toll free number 888-396(b) (6)and enter the numeric Passcode (b) (6) (# when prompted). (The USA Toll Number is +1-210-839-(b) (6).** The leader of the call is Dr. Abhik Das. The agenda, list of participants and material to be discussed will be sent by Fed-Ex on December 6th. Please let me know if you do **not** receive this material.

Thank you.
Betty

Betty Hastings

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Daily FiO2 values for first 14 days of life
Average daily FiO2 for each infant (average of 3 FiO2 measurements on SUPP05)
Includes data on 154 infants (73 High target, 81 Low target) for whom pulse oximeter data is available
12-5-05

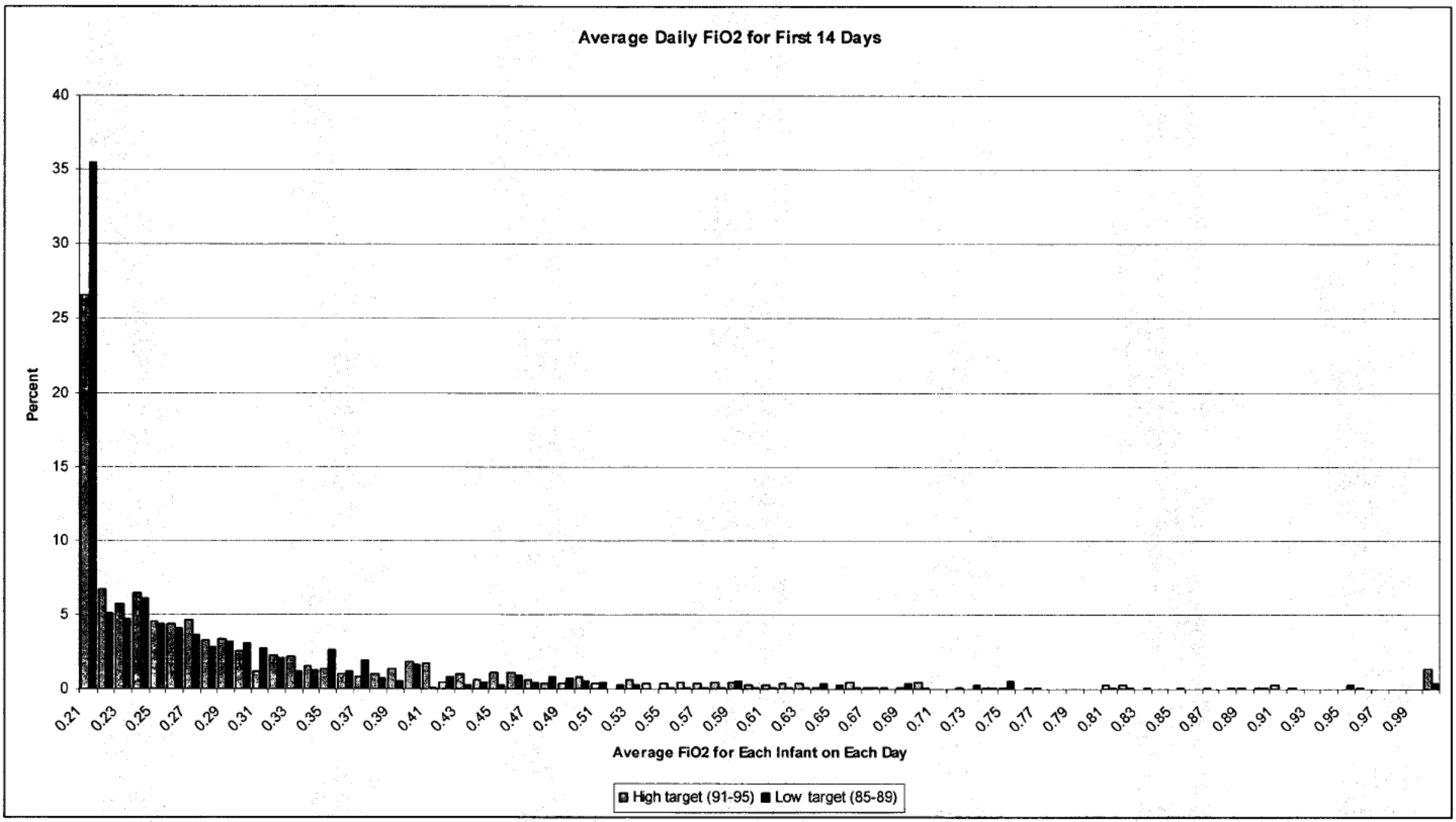
Summary statistics

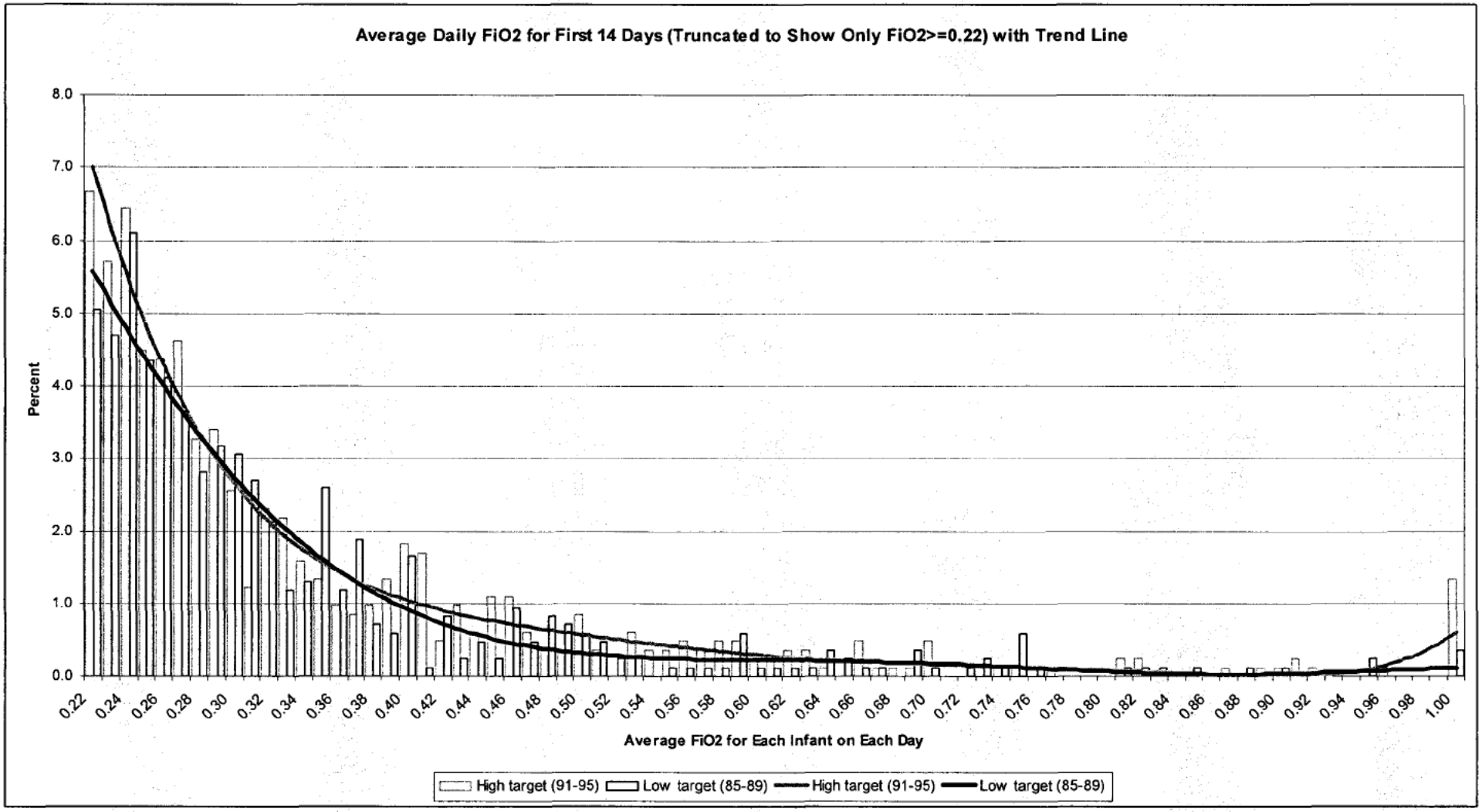
FiO2	High target (91-95)	Low target (85-89)
Mean	0.315	0.294
Maximum	1.000	1.000
90th percentile	0.500	0.447
75th percentile	0.466	0.317
Median	0.260	0.247
25th percentile	0.213	0.210
10th percentile	0.210	0.210
Minimum	0.210	0.210

Full distribution

Daily average FiO2 (interval lower bound)	High target (91-95)		Low target (85-89)	
	Percent	Cumulative	Percent	Cumulative
0.21	26.6	26.6	35.5	35.5
0.22	6.7	33.3	5.1	40.5
0.23	5.7	39.0	4.7	45.2
0.24	6.4	45.4	6.1	51.4
0.25	4.5	49.9	4.3	55.7
0.26	4.4	54.2	4.1	59.8
0.27	4.6	58.9	3.6	63.5
0.28	3.3	62.1	2.8	66.3
0.29	3.4	65.5	3.2	69.4
0.30	2.5	68.1	3.1	72.5
0.31	1.2	69.3	2.7	75.2
0.32	2.3	71.6	2.1	77.3
0.33	2.2	73.8	1.2	78.5
0.34	1.6	75.4	1.3	79.8
0.35	1.3	76.7	2.6	82.4
0.36	1.0	77.7	1.2	83.5
0.37	0.8	78.5	1.9	85.4
0.38	1.0	79.5	0.7	86.1
0.39	1.3	80.8	0.6	86.7
0.40	1.8	82.6	1.6	88.4
0.41	1.7	84.3	0.1	88.5
0.42	0.5	84.8	0.8	89.3
0.43	1.0	85.8	0.2	89.5
0.44	0.6	86.4	0.5	90.0
0.45	1.1	87.5	0.2	90.2
0.46	1.1	88.6	0.9	91.2
0.47	0.6	89.2	0.5	91.7
0.48	0.4	89.6	0.8	92.5
0.49	0.4	89.9	0.7	93.2
0.50	0.8	90.8	0.6	93.8
0.51	0.4	91.1	0.5	94.2

0.52	0.0	91.1	0.2	94.5
0.53	0.6	91.7	0.2	94.7
0.54	0.4	92.1	0.0	94.7
0.55	0.4	92.5	0.1	94.8
0.56	0.5	93.0	0.1	94.9
0.57	0.4	93.3	0.1	95.1
0.58	0.5	93.8	0.1	95.2
0.59	0.5	94.3	0.6	95.8
0.60	0.2	94.5	0.1	95.9
0.61	0.2	94.8	0.1	96.0
0.62	0.4	95.1	0.1	96.1
0.63	0.4	95.5	0.1	96.2
0.64	0.1	95.6	0.4	96.6
0.65	0.0	95.6	0.2	96.8
0.66	0.5	96.1	0.1	96.9
0.67	0.1	96.2	0.1	97.1
0.68	0.1	96.4	0.0	97.1
0.69	0.1	96.5	0.4	97.4
0.70	0.5	97.0	0.1	97.5
0.71	0.0	97.0	0.0	97.5
0.72	0.0	97.0	0.1	97.6
0.73	0.0	97.0	0.2	97.9
0.74	0.1	97.1	0.1	98.0
0.75	0.1	97.2	0.6	98.6
0.76	0.0	97.2	0.1	98.7
0.77	0.1	97.3	0.0	98.7
0.78	0.0	97.3	0.0	98.7
0.79	0.0	97.3	0.0	98.7
0.80	0.0	97.3	0.0	98.7
0.81	0.2	97.6	0.1	98.8
0.82	0.2	97.8	0.1	98.9
0.83	0.0	97.8	0.1	99.1
0.84	0.0	97.8	0.0	99.1
0.85	0.0	97.8	0.1	99.2
0.86	0.0	97.8	0.0	99.2
0.87	0.1	97.9	0.0	99.2
0.88	0.0	97.9	0.1	99.3
0.89	0.1	98.1	0.0	99.3
0.90	0.1	98.2	0.1	99.4
0.91	0.2	98.4	0.0	99.4
0.92	0.1	98.5	0.0	99.4
0.93	0.0	98.5	0.0	99.4
0.94	0.0	98.5	0.0	99.4
0.95	0.0	98.5	0.2	99.6
0.96	0.1	98.7	0.0	99.6
0.97	0.0	98.7	0.0	99.6
0.98	0.0	98.7	0.0	99.6
0.99	0.0	98.7	0.0	99.6
1.00	1.3	100.0	0.4	100.0





Daily FiO2 values for first 14 days of life (FiO2>=0.22 only)
Average daily FiO2 for each infant (average of 3 FiO2 measurements on SUPP05)
Includes data on 147 infants (71 High target, 76 Low target) for whom pulse oximeter data is available 12-5-05

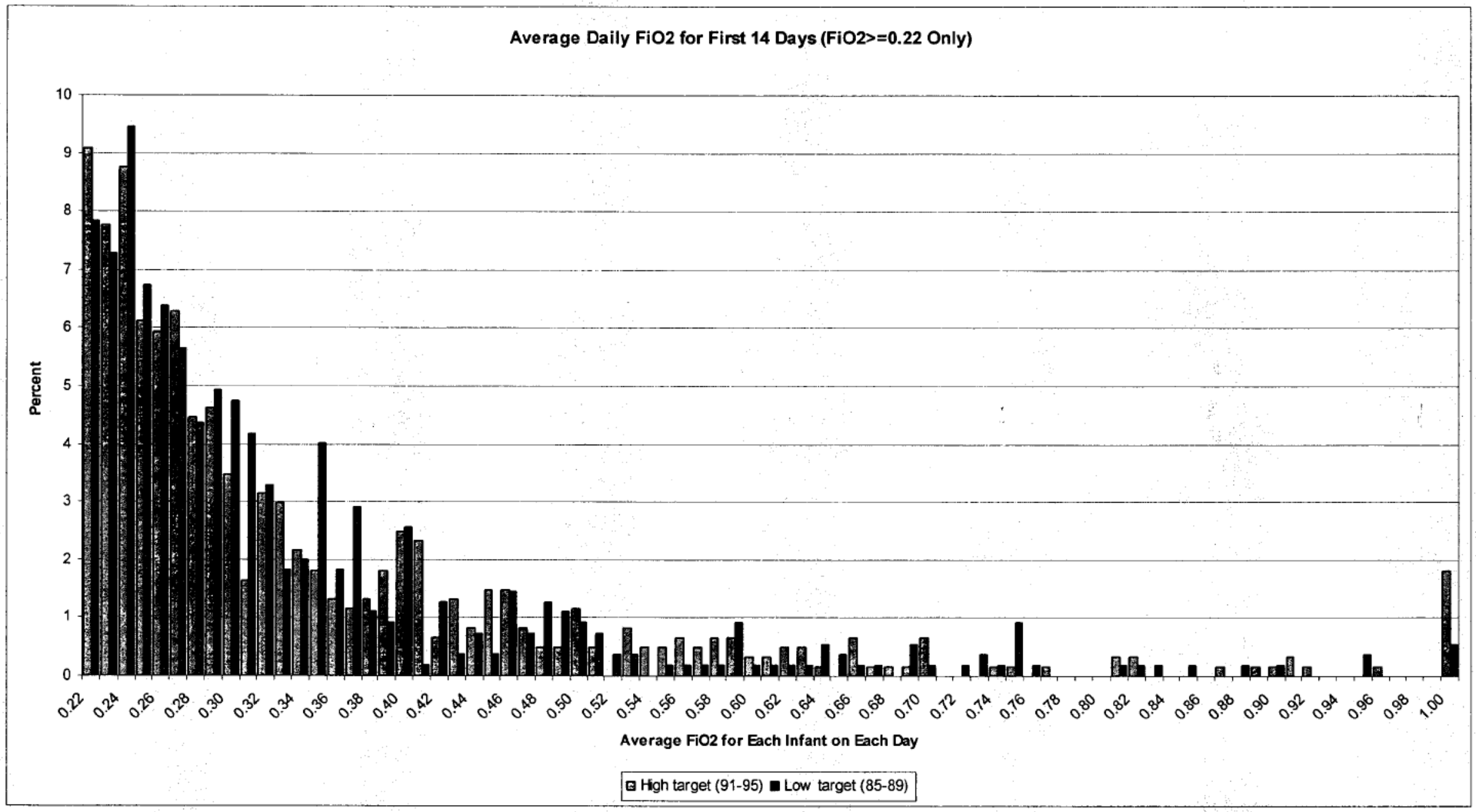
Summary statistics

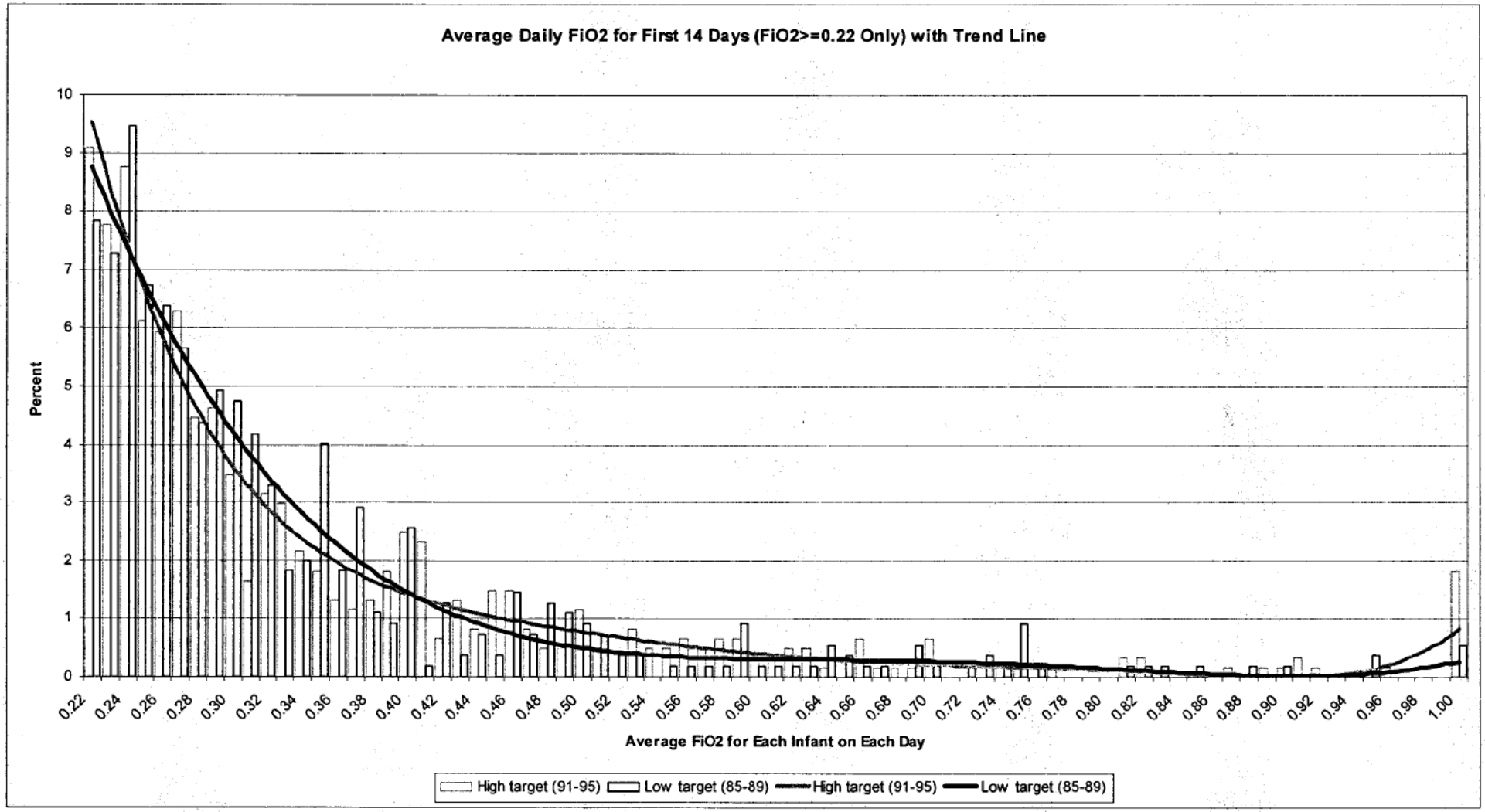
FiO2	High target (91-95)	Low target (85-89)
Mean	0.353	0.340
Maximum	1.000	1.000
90th percentile	0.563	0.503
75th percentile	0.400	0.370
Median	0.290	0.293
25th percentile	0.246	0.250
10th percentile	0.230	0.230
Minimum	0.220	0.220

Full distribution

FiO2	High target (91-95)		Low target (85-89)	
(interval lower bound)	Percent	Cumulative	Percent	Cumulative
0.22	9.09	9.1	7.83	7.8
0.23	7.77	16.9	7.29	15.1
0.24	8.76	25.6	9.47	24.6
0.25	6.12	31.7	6.74	31.3
0.26	5.95	37.7	6.38	37.7
0.27	6.28	44.0	5.65	43.4
0.28	4.46	48.4	4.37	47.7
0.29	4.63	53.1	4.92	52.6
0.30	3.47	56.5	4.74	57.4
0.31	1.65	58.2	4.19	61.6
0.32	3.14	61.3	3.28	64.8
0.33	2.98	64.3	1.82	66.7
0.34	2.15	66.4	2.00	68.7
0.35	1.82	68.3	4.01	72.7
0.36	1.32	69.6	1.82	74.5
0.37	1.16	70.7	2.91	77.4
0.38	1.32	72.1	1.09	78.5
0.39	1.82	73.9	0.91	79.4
0.40	2.48	76.4	2.55	82.0
0.41	2.31	78.7	0.18	82.1
0.42	0.66	79.3	1.28	83.4
0.43	1.32	80.7	0.36	83.8
0.44	0.83	81.5	0.73	84.5
0.45	1.49	83.0	0.36	84.9
0.46	1.49	84.5	1.46	86.3
0.47	0.83	85.3	0.73	87.1
0.48	0.50	85.8	1.28	88.3
0.49	0.50	86.3	1.09	89.4
0.50	1.16	87.4	0.91	90.3
0.51	0.50	87.9	0.73	91.1
0.52	0.00	87.9	0.36	91.4
0.53	0.83	88.8	0.36	91.8
0.54	0.50	89.3	0.00	91.8

0.55	0.50	89.8	0.18	92.0
0.56	0.66	90.4	0.18	92.2
0.57	0.50	90.9	0.18	92.3
0.58	0.66	91.6	0.18	92.5
0.59	0.66	92.2	0.91	93.4
0.60	0.33	92.6	0.18	93.6
0.61	0.33	92.9	0.18	93.8
0.62	0.50	93.4	0.18	94.0
0.63	0.50	93.9	0.18	94.2
0.64	0.17	94.0	0.55	94.7
0.65	0.00	94.0	0.36	95.1
0.66	0.66	94.7	0.18	95.3
0.67	0.17	94.9	0.18	95.4
0.68	0.17	95.0	0.00	95.4
0.69	0.17	95.2	0.55	96.0
0.70	0.66	95.9	0.18	96.2
0.71	0.00	95.9	0.00	96.2
0.72	0.00	95.9	0.18	96.4
0.73	0.00	95.9	0.36	96.7
0.74	0.17	96.0	0.18	96.9
0.75	0.17	96.2	0.91	97.8
0.76	0.00	96.2	0.18	98.0
0.77	0.17	96.4	0.00	98.0
0.78	0.00	96.4	0.00	98.0
0.79	0.00	96.4	0.00	98.0
0.80	0.00	96.4	0.00	98.0
0.81	0.33	96.7	0.18	98.2
0.82	0.33	97.0	0.18	98.4
0.83	0.00	97.0	0.18	98.5
0.84	0.00	97.0	0.00	98.5
0.85	0.00	97.0	0.18	98.7
0.86	0.00	97.0	0.00	98.7
0.87	0.17	97.2	0.00	98.7
0.88	0.00	97.2	0.18	98.9
0.89	0.17	97.4	0.00	98.9
0.90	0.17	97.5	0.18	99.1
0.91	0.33	97.9	0.00	99.1
0.92	0.17	98.0	0.00	99.1
0.93	0.00	98.0	0.00	99.1
0.94	0.00	98.0	0.00	99.1
0.95	0.00	98.0	0.36	99.5
0.96	0.17	98.2	0.00	99.5
0.97	0.00	98.2	0.00	99.5
0.98	0.00	98.2	0.00	99.5
0.99	0.00	98.2	0.00	99.5
1.00	1.82	100.0	0.55	100.0





From: Neil Finer
To: ccole@bidmc.harvard.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Trial
Date: Tuesday, December 06, 2005 2:16:18 PM

Hi Cindy
I will be able to talk to you hopefully later next week about SUPPORT. We are on a hold from the DSMC and will be having a meeting with them next week. Once that is done and we have a decision, I will call. Sorry that I am unable to discuss in any detail at present.
You will probably learn more from others than I am able to discuss at present.
Be well
Neil

-----Original Message-----
From: ccole@bidmc.harvard.edu [mailto:ccole@bidmc.harvard.edu]
Sent: Sunday, December 04, 2005 3:56 PM
To: nfiner@ucsd.edu
Subject: SUPPORT Trial
Importance: High

Dear Neil,
I realize am not up on the progress of SUPPORT.
The comment from Augusta (in the email below) is very important.
If you do not mind sharing, and if Augusta's comment is true, I would like to learn what issues put SUPPORT on hold, and if the issues are relevant to US POST, BOOST, etc.
I am in Wash DC.
Email you have.
Cell: 617-529(b) (6)
I hope you are well.
Look forward to speaking with you.
- Cindy

-----Original Message-----
From: Augusto Sola [mailto:augusto_sola@oz.ped.emory.edu]
Sent: Saturday, December 03, 2005 5:31 PM
To: Maribeth Sayre
Cc: Valerie Begnoche; """ <ccole@bidmc.harvard.edu>,"Roger.Wu" <RWu@masimo.com>, "Joe.Kiani" <kiani@masimo.com>,"Mike.Petterson" <MPetters@masimo.com>"@virginia.cc.emory.edu
Subject: Re: Masimo Holiday Card

Of course my study can be referenced if done appropriately.
SUPPORT has already been put on hold due to poor design (as suggested)
Thank you
Augusto
Maribeth Sayre <MSayre@masimo.com> on Friday, December 02, 2005 at 2:39 PM
+0000 wrote:
>Hi Valerie,
>

>Since the SUPPORT and BOOST II studies are just getting underway, and we
>will not have information about the outcomes of these studies for several
>years, I would suggest we NOT reference ROP on our cards at this time.
>
>Maribeth
>
>
>-----Original Message-----
>From: Valerie Begnoche
>Sent: Friday, December 02, 2005 10:02 AM
>To: 'ccole@bidmc.harvard.edu'; 'augusto_sola@oz.ped.emory.edu'; Maribeth
>Sayre
>Cc: Roger Wu
>Subject: Masimo Holiday Card
>
>
>Dear Colleagues:
>Masimo is considering including a message in our holiday card that makes
>reference to Dr. Sola's study on ROP. Please let us know if you have any
>concerns or objections about the message.
>
>Regards,
>Valerie Begnoche
>for Joe Kiani
>

From:	Neil Finer
To:	"Hastings, Betty J."
Cc:	nfiner@ucsd.edu; "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Das, Abhik"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Maynard Rasmussen"; "Michele"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Subject:	FW:
Date:	Monday, December 05, 2005 11:48:30 PM
Attachments:	Daily FiO2 for first 14 days.doc Response to DSMC Steering Dec 5.doc Avery Letter Dec 05.doc 20040226AVIOxLateBreakerDraft.doc Percent of time spent at each SpO2 value 12-2-05.doc Askie NEJM.pdf STOP-ROP.pdf ucsd Conversion.doc

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Hi Betty
Thanks for being patient
These are the actual files that should be sent to the DSMC. I have reread them and made some additional changes to the crucial files: ie the Response to the DSMC and the Avery Letter are not the same as the ones that were previously circulated.
Please let me know if you have any difficulty opening or sending these.
I have waited till 11:00PM Eastern Time for any further responses.
I think that we should go with these and give the DSMC time to review.
Be well
Neil

Daily FiO2 values for first 14 days of life
Average daily FiO2 for each infant (average of 3 FiO2 measurements on SUPP05)
Includes data on 155 infants (73 High target, 82 Low target) for whom pulse oximeter data is available
12-5-05

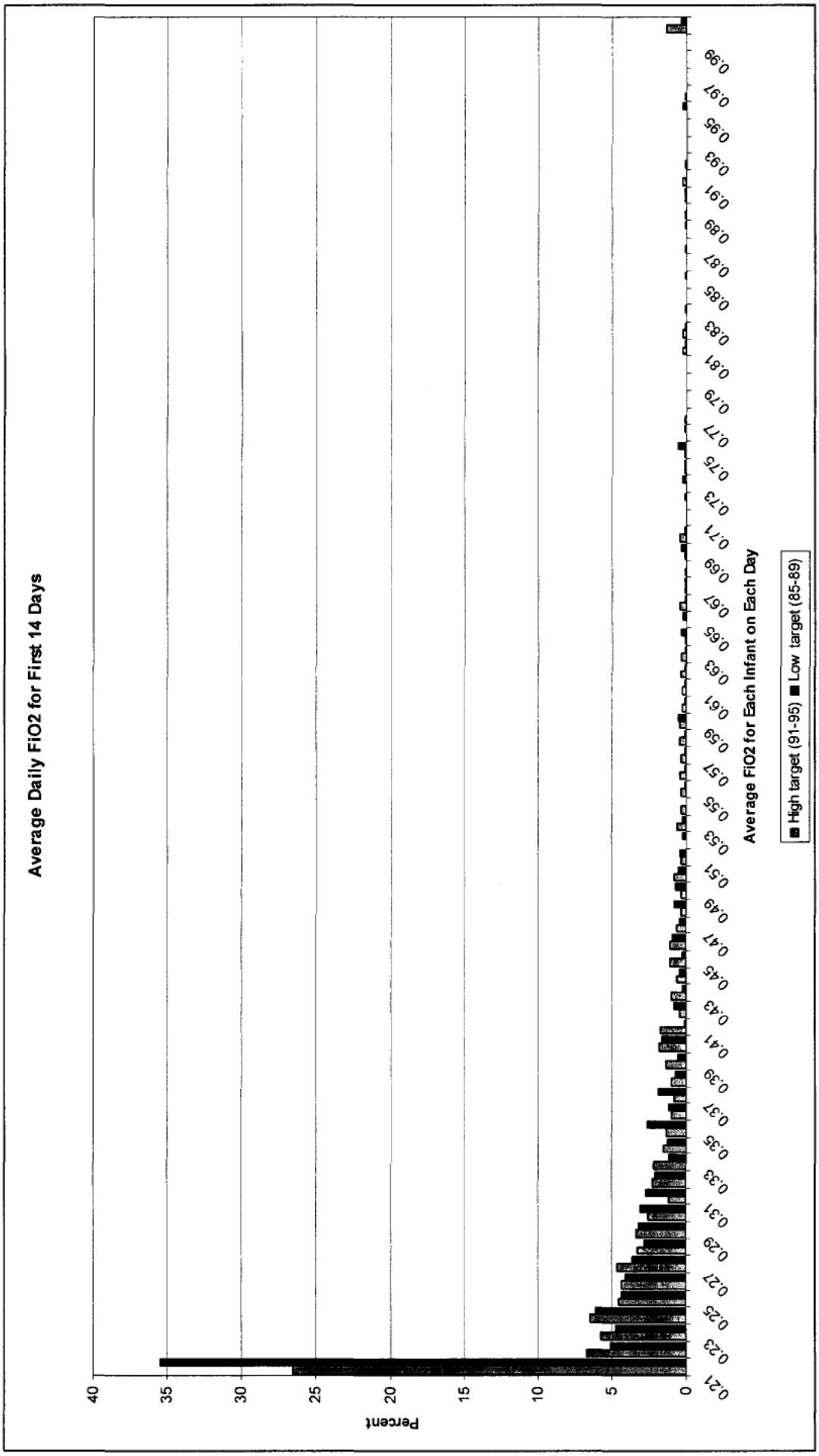
Summary statistics

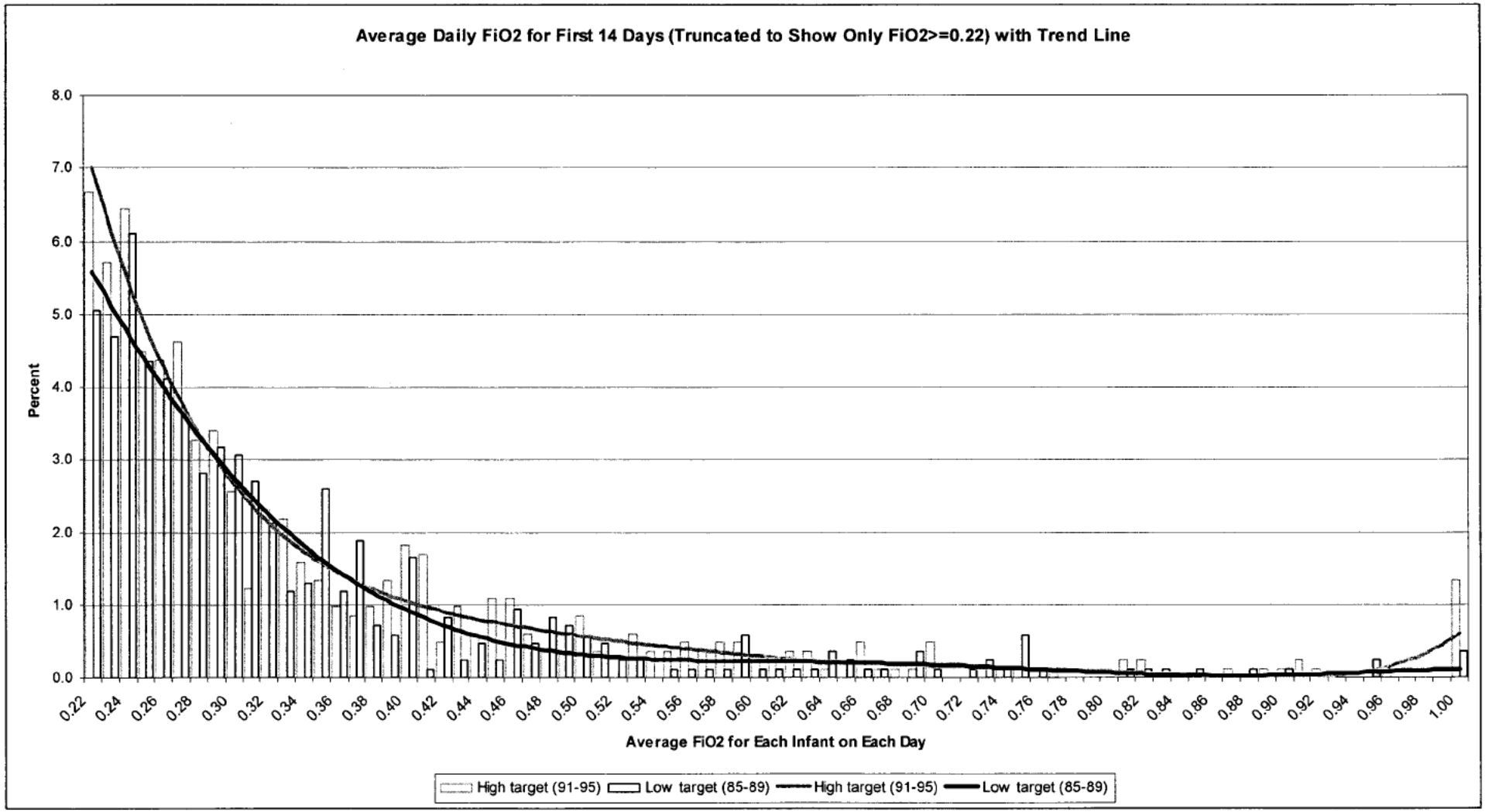
FiO2	High target (91-95)	Low target (85-89)
Mean	0.315	0.294
Maximum	1.000	1.000
90th percentile	0.500	0.447
75th percentile	0.466	0.317
Median	0.260	0.247
25th percentile	0.213	0.210
10th percentile	0.210	0.210
Minimum	0.210	0.210

Full distribution

Daily average FiO2 (interval lower bound)	High target (91-95)		Low target (85-89)	
	Percent	Cumulative	Percent	Cumulative
0.21	26.6	26.6	35.5	35.5
0.22	6.7	33.3	5.1	40.5
0.23	5.7	39.0	4.7	45.2
0.24	6.4	45.4	6.1	51.4
0.25	4.5	49.9	4.3	55.7
0.26	4.4	54.2	4.1	59.8
0.27	4.6	58.9	3.6	63.5
0.28	3.3	62.1	2.8	66.3
0.29	3.4	65.5	3.2	69.4
0.30	2.5	68.1	3.1	72.5
0.31	1.2	69.3	2.7	75.2
0.32	2.3	71.6	2.1	77.3
0.33	2.2	73.8	1.2	78.5
0.34	1.6	75.4	1.3	79.8
0.35	1.3	76.7	2.6	82.4
0.36	1.0	77.7	1.2	83.5
0.37	0.8	78.5	1.9	85.4
0.38	1.0	79.5	0.7	86.1
0.39	1.3	80.8	0.6	86.7
0.40	1.8	82.6	1.6	88.4
0.41	1.7	84.3	0.1	88.5
0.42	0.5	84.8	0.8	89.3
0.43	1.0	85.8	0.2	89.5
0.44	0.6	86.4	0.5	90.0
0.45	1.1	87.5	0.2	90.2
0.46	1.1	88.6	0.9	91.2
0.47	0.6	89.2	0.5	91.7
0.48	0.4	89.6	0.8	92.5
0.49	0.4	89.9	0.7	93.2
0.50	0.8	90.8	0.6	93.8
0.51	0.4	91.1	0.5	94.2

0.52	0.0	91.1	0.2	94.5
0.53	0.6	91.7	0.2	94.7
0.54	0.4	92.1	0.0	94.7
0.55	0.4	92.5	0.1	94.8
0.56	0.5	93.0	0.1	94.9
0.57	0.4	93.3	0.1	95.1
0.58	0.5	93.8	0.1	95.2
0.59	0.5	94.3	0.6	95.8
0.60	0.2	94.5	0.1	95.9
0.61	0.2	94.8	0.1	96.0
0.62	0.4	95.1	0.1	96.1
0.63	0.4	95.5	0.1	96.2
0.64	0.1	95.6	0.4	96.6
0.65	0.0	95.6	0.2	96.8
0.66	0.5	96.1	0.1	96.9
0.67	0.1	96.2	0.1	97.1
0.68	0.1	96.4	0.0	97.1
0.69	0.1	96.5	0.4	97.4
0.70	0.5	97.0	0.1	97.5
0.71	0.0	97.0	0.0	97.5
0.72	0.0	97.0	0.1	97.6
0.73	0.0	97.0	0.2	97.9
0.74	0.1	97.1	0.1	98.0
0.75	0.1	97.2	0.6	98.6
0.76	0.0	97.2	0.1	98.7
0.77	0.1	97.3	0.0	98.7
0.78	0.0	97.3	0.0	98.7
0.79	0.0	97.3	0.0	98.7
0.80	0.0	97.3	0.0	98.7
0.81	0.2	97.6	0.1	98.8
0.82	0.2	97.8	0.1	98.9
0.83	0.0	97.8	0.1	99.1
0.84	0.0	97.8	0.0	99.1
0.85	0.0	97.8	0.1	99.2
0.86	0.0	97.8	0.0	99.2
0.87	0.1	97.9	0.0	99.2
0.88	0.0	97.9	0.1	99.3
0.89	0.1	98.1	0.0	99.3
0.90	0.1	98.2	0.1	99.4
0.91	0.2	98.4	0.0	99.4
0.92	0.1	98.5	0.0	99.4
0.93	0.0	98.5	0.0	99.4
0.94	0.0	98.5	0.0	99.4
0.95	0.0	98.5	0.2	99.6
0.96	0.1	98.7	0.0	99.6
0.97	0.0	98.7	0.0	99.6
0.98	0.0	98.7	0.0	99.6
0.99	0.0	98.7	0.0	99.6
1.00	1.3	100.0	0.4	100.0





Daily FiO2 values for first 14 days of life (FiO2>=0.22 only)
Average daily FiO2 for each infant (average of 3 FiO2 measurements on SUPP05)
Includes data on 148 infants (71 High target, 77 Low target) for whom pulse oximeter data is available
12-5-05

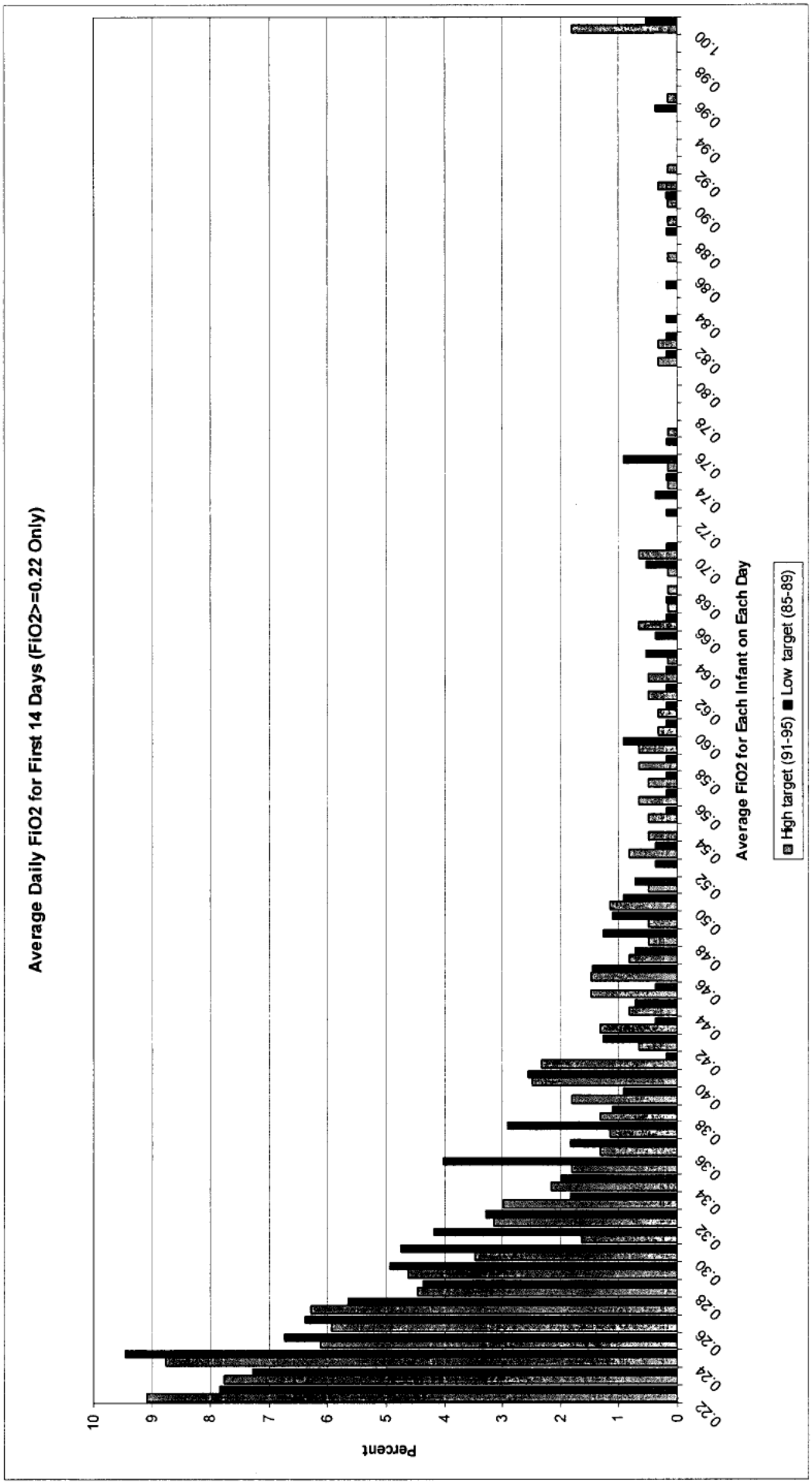
Summary statistics

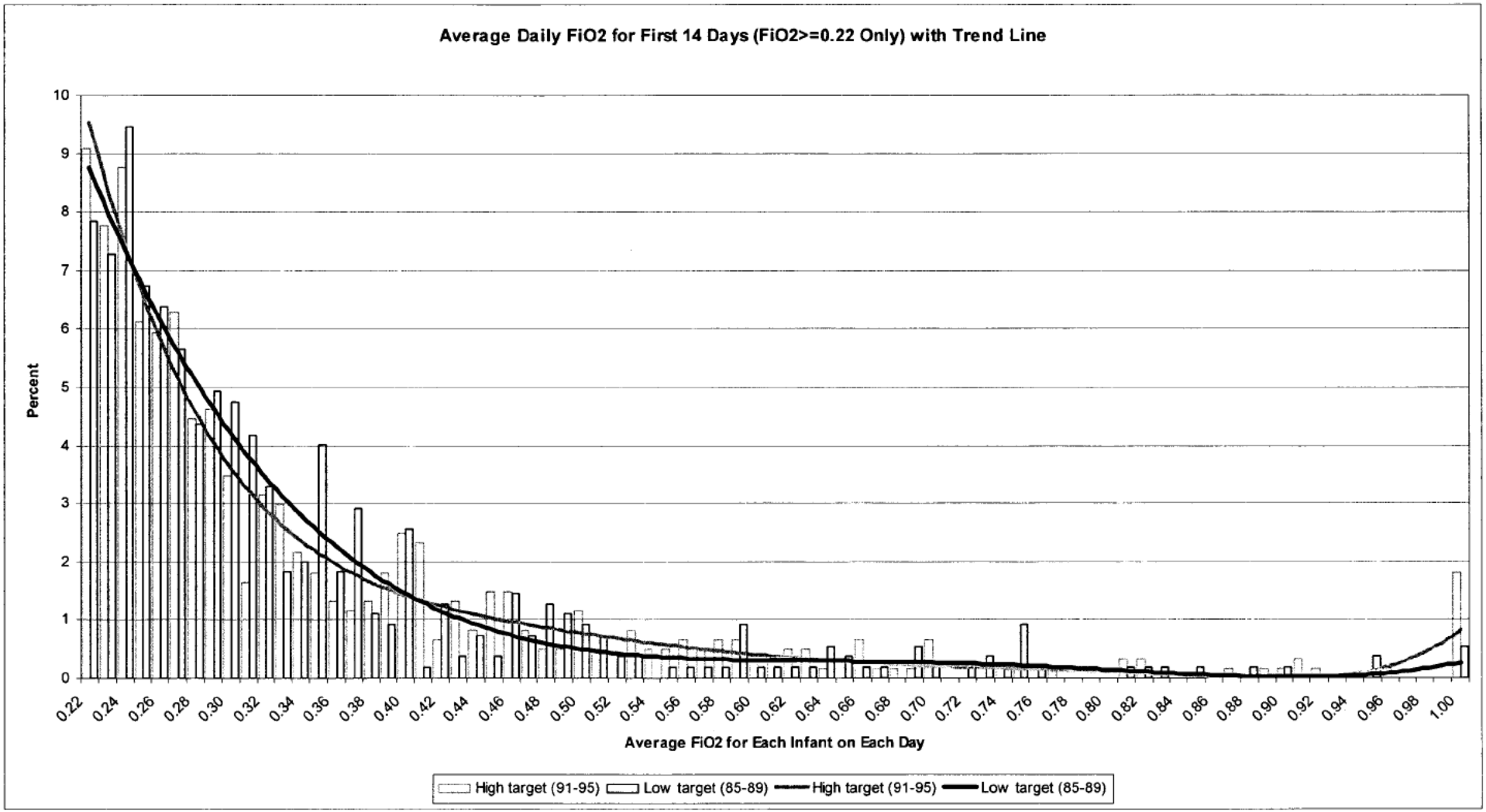
FiO2	High target (91-95)	Low target (85-89)
Mean	0.353	0.340
Maximum	1.000	1.000
90th percentile	0.563	0.503
75th percentile	0.400	0.370
Median	0.290	0.293
25th percentile	0.246	0.250
10th percentile	0.230	0.230
Minimum	0.220	0.220

Full distribution

FiO2	High target (91-95)		Low target (85-89)	
(interval lower bound)	Percent	Cumulative	Percent	Cumulative
0.22	9.09	9.1	7.83	7.8
0.23	7.77	16.9	7.29	15.1
0.24	8.76	25.6	9.47	24.6
0.25	6.12	31.7	6.74	31.3
0.26	5.95	37.7	6.38	37.7
0.27	6.28	44.0	5.65	43.4
0.28	4.46	48.4	4.37	47.7
0.29	4.63	53.1	4.92	52.6
0.30	3.47	56.5	4.74	57.4
0.31	1.65	58.2	4.19	61.6
0.32	3.14	61.3	3.28	64.8
0.33	2.98	64.3	1.82	66.7
0.34	2.15	66.4	2.00	68.7
0.35	1.82	68.3	4.01	72.7
0.36	1.32	69.6	1.82	74.5
0.37	1.16	70.7	2.91	77.4
0.38	1.32	72.1	1.09	78.5
0.39	1.82	73.9	0.91	79.4
0.40	2.48	76.4	2.55	82.0
0.41	2.31	78.7	0.18	82.1
0.42	0.66	79.3	1.28	83.4
0.43	1.32	80.7	0.36	83.8
0.44	0.83	81.5	0.73	84.5
0.45	1.49	83.0	0.36	84.9
0.46	1.49	84.5	1.46	86.3
0.47	0.83	85.3	0.73	87.1
0.48	0.50	85.8	1.28	88.3
0.49	0.50	86.3	1.09	89.4
0.50	1.16	87.4	0.91	90.3
0.51	0.50	87.9	0.73	91.1
0.52	0.00	87.9	0.36	91.4
0.53	0.83	88.8	0.36	91.8
0.54	0.50	89.3	0.00	91.8

0.55	0.50	89.8	0.18	92.0
0.56	0.66	90.4	0.18	92.2
0.57	0.50	90.9	0.18	92.3
0.58	0.66	91.6	0.18	92.5
0.59	0.66	92.2	0.91	93.4
0.60	0.33	92.6	0.18	93.6
0.61	0.33	92.9	0.18	93.8
0.62	0.50	93.4	0.18	94.0
0.63	0.50	93.9	0.18	94.2
0.64	0.17	94.0	0.55	94.7
0.65	0.00	94.0	0.36	95.1
0.66	0.66	94.7	0.18	95.3
0.67	0.17	94.9	0.18	95.4
0.68	0.17	95.0	0.00	95.4
0.69	0.17	95.2	0.55	96.0
0.70	0.66	95.9	0.18	96.2
0.71	0.00	95.9	0.00	96.2
0.72	0.00	95.9	0.18	96.4
0.73	0.00	95.9	0.36	96.7
0.74	0.17	96.0	0.18	96.9
0.75	0.17	96.2	0.91	97.8
0.76	0.00	96.2	0.18	98.0
0.77	0.17	96.4	0.00	98.0
0.78	0.00	96.4	0.00	98.0
0.79	0.00	96.4	0.00	98.0
0.80	0.00	96.4	0.00	98.0
0.81	0.33	96.7	0.18	98.2
0.82	0.33	97.0	0.18	98.4
0.83	0.00	97.0	0.18	98.5
0.84	0.00	97.0	0.00	98.5
0.85	0.00	97.0	0.18	98.7
0.86	0.00	97.0	0.00	98.7
0.87	0.17	97.2	0.00	98.7
0.88	0.00	97.2	0.18	98.9
0.89	0.17	97.4	0.00	98.9
0.90	0.17	97.5	0.18	99.1
0.91	0.33	97.9	0.00	99.1
0.92	0.17	98.0	0.00	99.1
0.93	0.00	98.0	0.00	99.1
0.94	0.00	98.0	0.00	99.1
0.95	0.00	98.0	0.36	99.5
0.96	0.17	98.2	0.00	99.5
0.97	0.00	98.2	0.00	99.5
0.98	0.00	98.2	0.00	99.5
0.99	0.00	98.2	0.00	99.5
1.00	1.82	100.0	0.55	100.0





In response to the comments and concerns of the DSMC, the SUPPORT committee held a conference call Monday Nov 28th at 10:00 to 1130AM to prepare a response. This issue and the preparation of a response was then discussed by the entire NICHD Neonatal Research Network Steering Committee in a conference call held Wednesday. Nov 30th at 9:30 – 11:00 AM. This response has been reviewed by the SUPPORT Subcommittee, and subsequently by the Steering Committee, and reflects the input of all NICHD Principal Investigators.

- The DSMC made the following 2 comments in their letter regarding the SUPPORT trial. This was generated after they reviewed the oximeter data, which was corrected back to actual SpO2 values from the altered values displayed at the bedside:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

We have responded to each of these concerns and our responses are detailed below

Response to Issue Number 1

We appreciate the concern expressed by the DSMC regarding a potential safety issue secondary to durations of SpO2 values greater than 95%.

1. Review of existing evidence and practice regarding durations of higher SpO2 values:

To date there are no prospective data which define the SpO2s experienced by the ELBW infant from birth as part of usual clinical care. Because no published studies have evaluated the effects of different target SpO2 ranges from birth on important outcomes, this was one of the principle reasons for the design and conduct of the SUPPORT trial – Oximeter Arm.

A number of studies have evaluated different alarm limits, but have not reported the actual durations of SpO2 in the various ranges. Nghiem et al in a PAS abstract this year reported that nurses caring for ELBW infants believe that an acceptable oxygen saturation range should include higher upper limits than

specified by current policy (Nghiem et al, Nursing Opinions and Practices of Oxygenation in Prematures: The NOPOP Study PAS #3415, 2005). The study by Hagadorn reported as a late breaker at the PAS last year (Hagadorn et al, Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation. PAS 2004, Attached) did report on the experience of monitoring the actual SpO2 for 72 hours in the first 4 weeks of life in 78 ELBW infants. They reported that the "lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for a median of 70 hours (25th-75th percentiles 67-71 hr) during each of the first 24 weeks. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25th-75th percentiles 91-97%; range of study center medians 91-96%. Centers ranged between 16-71% compliance with their individual intended SpO2 range. Most noncompliance was above intended range." In comparing the SUPPORT data evaluated to date by the DSMC, it is of interest that the mean SpO2 in the 2 Oximeter arms is 90% and 92%, with medians of 92% and 94%, all of which are below that reported by Hagadorn et al (median=95%).

The 2 other relevant trials, STOP-ROP and BOOST, both enrolled infants of > 32 weeks postmenstrual age (PMA), and maintained 2 levels of SpO2, 89% to 94% and 91 to 94% versus 95% to 98% and 96% to 99%, by administration of oxygen. These studies achieved reasonable separation, but did demonstrate substantial overlap of the intended ranges (estimated to be 50% or greater, D Phelps, PI for STOP-ROP). It is important to note that these studies were testing two ranges both of which were higher than the lower range of the SUPPORT trial (85% to 89%) and were treating infants who, for the most part, had recovered from their acute disease. In the BOOST trial 70% of the enrolled infants were < 28 weeks of age at birth (all of SUPPORT is < 28 weeks), 32 weeks PMA at enrollment, and required oxygen at enrollment (Askie et al, New England Journal of Medicine. 2003; 349(10):959-967). The STOP-ROP trial enrolled infants with pre-threshold ROP at a PMA of 35.4 + 2.5 weeks of age (Phelps et al, Pediatrics. 2000; 105(2):295-310). These trials then gave the higher SpO2 range infants additional oxygen to increase their SpO2 to the desired range. STOP-ROP reported that the infants in the high range had an SpO2 > 95% for > 97% of the monitored time. These studies found an overall increase in pulmonary morbidity in the higher SpO2 range infants.

Examination of oximeter data from one of the NRN sites (Case Western, Walsh et al) obtained for a current ongoing study evaluating infants similar to those enrolled in SUPPORT, and managed with conventional oximeters, revealed that for the 9 infants for whom results were available that the percentage of time with and SpO2 > 95% was > 50%.

2. Impact of SUPPORT oximeters algorithm on sat values:

The oximetry algorithm that was designed for the SUPPORT trial is such that re-conversion of the altered oximeter values does not result in a discrete SpO2 number for every displayed value. SpO2 values, of 93%, 94% 95% and 96% will all be reconverted to a single value. In the 85% to 89% arm, values of 84%, 85%, 86% and 87% will be reconverted to a single value of 84%. This is a

result of having the displayed values return to non-skewed SpO2 values at < 84% and > 96%, a safety design felt to be important by all involved in this trial (See Attached file USCD Conversion). Thus the percentages reported to the DSMC for some of the ranges that include these values were not an accurate representation of the true values. However all values > 96% and < 84% are actual and do not require any conversion.

Percent of time of spent at SpO2 < 84% and > 96%
(RTI, Dec 2, 2005)

Range **Assigned**	High target (91-95)	Low target (85-89)
< 84%	8.30	14.05
> 96%	21.45	15.47

In the current SUPPORT study, an initial analyses utilizing only unaltered SpO2 values as shown above , ie those below 84% and above 96%, have shown that one arm had an SpO2 > 96% for 15.47% versus 21.45% of the time for the comparison arm, and the duration of an SpO2 < 84% was also different at 14.05% versus 8.30%. The values for SpO2s > 96% using unaltered data suggests that the SUPPORT trial to date has, if anything, reduced the duration of higher oxygen saturations.

In addition, analyses using only actual SpO2 demonstrate that the infants in this trial who are receiving supplemental oxygen are spending approximately 70% of the time with a true SpO2 value between 84% and 96%. We believe that this is information is very encouraging.

3. Impact of inclusion of data from periods in room air on saturation distributions:

As part of the SUPPORT trial, we collect information about inhaled oxygen concentration 3 times a day for the first 14 days and daily thereafter. We believe that an improved documentation of the times when infants are actually on room air will allow us to determine the saturations during actual oxygen exposure. At the present an infant is considered to be receiving supplemental oxygen if he/she requires oxygen for greater than 2 hours in a day. This results in infants being categorized as receiving supplemental oxygen for significant periods when they are actually in room air. This would result in durations of SpO2 greater than 95% that were felt to be modifiable and reported as such when in fact there is no effective treatment for such elevated SpO2s. In addition, we do not know if such SpO2s on room air are associated with any morbidity. From the SUPPORT study data analyses to date we know that study infants in room air have SpO2s > 95% for 46% to 69% of the time. By using only information for actual SpO2 values of 96%, we have determined that the infants in the 91%-95% group had a duration at an SpO2 of 96% of 6.68%, and a total duration of 96% or greater of 28.13%.

In view of this design, we would suggest that all future interval analyses for safety examine the ranges of <84% and >96% and consider those ranges for review of low and high durations of SpO2.

We believe that the SUPPORT trial will actually define the periods of time that ELBW infants spend with different ranges of SpO2, and that it is essential to collect this information. In addition, as our findings indicate a lower true percent of the time at SpO2 values >95%, and lower median SpO2 values than has previously been reported, we are in fact, reducing the time with high SpO2 values compared to usual care. The SUPPORT trial carefully evaluates risks, and we will be evaluating group differences for all important short and long term outcomes.

The SUPPORT trial methodology actively encourages all caretakers to keep SpO2 < 96% by having alarm limits set at 85% and 95%. These limits were utilized because it was felt that these represented current practice, and there are no studies which have provided information regarding durations of SpO2 below 85% and subsequent outcomes. While we have had substantial discussion about decreasing the lower alarm limit to below 84%, we are reluctant to make such a recommendation in view of the likely resultant increases in durations of SpO2 below 84%. Nevertheless, our results to date suggest that we have decreased the expected percent of time > 95%, and in one group the value of 14% may be as low as is achievable in an actual clinical environment given the evidence provided by Hagadorn et al and Nghiem et al. In addition a preliminary analysis of the FiO2 exposure of the 2 oximeter groups has demonstrated that the 85% - 89% group have a substantially decreased exposure to oxygen compared to the 91% - 95% group. (See below)

We believe the SUPPORT study will define the distribution and durations of pulse oximetry values among premature infants in highly staffed, dedicated academic centers, and among infants randomized to two different target ranges. For this reason alone, the SUPPORT trial will be very valuable. All of the procedures outlined below in response to your second concern will also allow us to further increase the percentage of time that the infants are in the maximally altered SpO2 ranges which we believe will further increase separation of these groups.

Response to Issue Number 2

There is concern that we have not achieved adequate separation by the current oximeters and study personnel.

1. As described above, the results of additional analyses performed in response to the concerns of the DSMC show differences in the durations of low and high SpO2s between the 2 oximeter groups, but lesser differences in the narrower target ranges. A careful analysis of the most recent converted values demonstrates that the cumulative time spent with an SpO2 of 90% or less is 24.0% (91% - 95%) versus 39.5% (85% - 89%,See Percent of time at each SpO2

value 12-2-05.doc). In addition, the 91% -95% group spend 40% of the time in that narrow range which may represent the achievable target duration for the narrow target range. The 85% - 89% oximeter group spends 18% of the time in their narrow target range. One obvious reason for this difference is that when the 91%-95% group exceeds the high end of the range, the oximeter alarms, whereas this does not occur for the high end of the lower range infants.

We have now had an opportunity to review the actual FiO2 exposure of the 2 oximeter groups and that analysis is attached (Daily FiO2 for first 14 days.doc). This analysis has shown that the infants in 85% - 89% group spend approximately 10% more time in room air in the first 14 days than infants in the 91% - 95% group (35.5% vs 26.6%). We do not at the present time have any comparative data for similar populations of ELBW infants, and the actual significance of these differences will only become apparent when the trial is completed.

2. We do acknowledge that it would be desirable to increase the percentage of time in the narrower target range and towards this end would propose the following changes to SUPPORT:

A. We will **change the high alarm to 94% to further assist in keeping the 85%- 89% group more in target and reduce the durations of SpO2 > 95% in the 91% - 95% group**. This change should improve our time in the narrow target ranges and further separate our 2 oximeter groups. For the 91%-95% group, at present when the study oximeter reads greater than 92%, the actual SpO2 is at 95%. This will result in more frequent high alarms for this group, the result of which will be to reduce the durations of higher SpO2s.

B. We will require **documentation that the oximeters alarm limits are set and functional as per protocol every 4- 6 hours**. We have found that in some units the high alarms are being turned off, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned to the most appropriate personnel in each unit, which may include bedside or research nurses or respiratory therapists, and this procedure is already being done in many NRN units.

C. We will immediately initiate a **change in our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect saturations measured while on oxygen therapy and exclude saturations of infants in room air.** We will change the data form to indicate that the infant was either in oxygen for the entire 24 hours, and if not, will provide a more accurate estimate of the true time in oxygen, and we will continue with this form of data collection for the entire time that the infant is receiving oxygen. In the current protocol we collect such information 3 times a day for the first 14 days only and then daily thereafter. We believe that more frequent and extended documentation will allow us to determine more accurately the actual time that an infant is in room air. At the present the infant is considered to have spent a day in oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized

in oxygen for significant periods when they are in room air. While in room air, we cannot manipulate the SpO2, and thus knowledge of the true time in oxygen will produce a more accurate representation of oximetry results that are subject to care interventions.

D. We will initiate **further training and in-service, and a change to the protocol to stress the importance of keeping the SpO2 alarms functional and at the limits of 85% and 94%**. In the past these were guidelines, and we will now change the study manual and protocol to indicate these limits are now set by protocol and that violations will be documented. We will encourage all caretakers to aim for an SpO2 value of 90% and make every effort to educate caretakers to make smaller adjustments in FiO2 and ensure that the infant is maintained between the 87% to 93%, the range with the maximal separation of the study oximeters. We will further facilitate the use of the 2 hour and 12 hour histograms showing the infants' actual ranges to provide feedback to the caretakers regarding the percentage of time in the target ranges.

E. We will develop **guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation**. More modulated increases in oxygen during these desaturation events will minimize overshoot and the potential of high SpO2 values. We would hope that such changes – ie increasing the FiO2 in steps of 5% as opposed to much larger increases will decrease the resultant overshoots creating the high SpO2 values. This will be included in the revised manual of operations.

F. **We will place bedside cards to indicate the desired target range**.

G. We will **initiate compliance monitoring visits coordinated by RTI to visit random sites**. These visits had been planned, but had not yet been initiated. The teams will consist of a member of RTI and a study coordinator, and they will review the adherence to the protocol and any other relevant issues.

H. We would recommend that at a minimum, **the unblinded oximetry data be reviewed again after an additional 100 to 150 infants have been enrolled in this trial.**

We thank the DSMC for their thoughtful concerns. We trust that our plans to move forward with the SUPPORT trial are acceptable to the DSMC. We are anxious to initiate the above changes, seek IRB approvals and re-activate this trial.

UNIVERSITY OF CALIFORNIA, SAN DIEGO UCSD

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December 05, 2005

Gordon Avery, M.D.
Chairman of the Data Safety Monitoring Committee
NICHD Neonatal Research Network

Dear Dr. Avery,

The SUPPORT Trial Subcommittee and the NICHD Network Steering Committee have reviewed in detail the concerns of the Data Safety Monitoring Committee. We are appreciative of the diligence and thoughtfulness that went into these concerns and we have carefully considered the comments made by the Data Safety Monitoring Committee with respect to both the issue of patient safety and the question of futility relative to the separation of the infants in the two oximetry arms of the trial.

We are very mindful of the need to protect patient safety and toward this end have reviewed the current experience relative to exposure of current ELBW infants to saturations above 95%. There is little information regarding this issue in the literature. We have quoted what we believe to be the relevant recent experiences, including the Network experience with exposures to higher SpO2 ranges. In addition we had asked RTI to provide us with unaltered oximetry data which allows us to look at information for oxygen saturations of 97% or greater and less than 84%, as these values were not altered by the algorithm in place for the study. We also compared the mean and median values of the SpO2 seen in the SUPPORT trial to date with those reported by Hagadorn et al, the only other report that contains such information. This information suggests that our current SpO2 exposures, especially to SpO2 values of 97% and above, for infants within the SUPPORT trial are probably less than is currently being experienced outside of the trial, both from the Network experience and in the general practice of neonatology for the ELBW infant. In addition our median SpO2 values for both of our oximetry groups are lower than those reported by Hagadorn et al. An initial evaluation of the FiO2 data does demonstrate that the 85%-89% group requires oxygen for 10% less overall duration in the first 14 days than the 91%-95% group, further indicating that these groups are being separated in their clinical management.

We agree that we should aim for greater separation between the oximetry groups, and are pleased that we are seeing some differences on SpO2 and FiO2 exposures between the groups. There is less separation in the target ranges than we desired, and I have detailed our responses to each of the

DSMC's concerns in the attached review. We believe that with these changes to the Protocol and Manual of operations and additional in-service at the sites coupled with intermittent site visits, that we will attain an even greater SpO2 separation in all ranges, and differential oxygen exposure for our 2 study groups. We would also like to recommend a re-evaluation of this data after an additional 100-150 infants have been enrolled.

We thank you and your committee for your careful review and suggestions. We hope that our responses are appropriate and that we may be allowed to continue this important trial

Sincerely,

Neil N. Finer, M.D.
Principal Investigator on behalf of the SUPPORT Subcommittee

LATE BREAKER ABSTRACT SUBMISSION FORM

Abstracts and Payment must be RECEIVED by March 1, 2004

~ Abstracts must be submitted electronically using this form.
~ Abstracts, inclusive of title, authors, institutions, and graphs/tables, must fit in a 6.5 inch x 4 inch space between the two lines (appx. 2,600 characters). Use a font no smaller than 10 pt.
~ You must complete all information and include payment ($50 US) for your abstract to be considered.

Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation

J Hagadorn [1,2], A Furey [1], TH Nghiem [1], S Greene [1], E Abban [1], J Cho [1], P Shrestha [1], A Vora [1], M Landa [2], C Schmid [2], P Hibberd [2], CH Cole [1] and The AVIOx Study Group. [1]Div Newborn Med and [2]Div of Clin Care Research, Tufts-New England Med Ctr, Boston, MA.

Background: Detailed data are not available regarding the actual versus intended SpO2 in infants born <28 weeks gestation (extremely premature newborns, EPNs) in the neonatal period during routine care. **Objective:** To document actual SpO2 in EPNs in the first 4 weeks of life during routine care and compare to the level recommended by local policy/guideline. **Design/Methods:** EPNs <96 hours old were enrolled in a prospective multicenter cohort study. Oximetry data were collected every 2 seconds with masked signal-extraction oximeters for 72 hours in each of the first four weeks of life. Data were compared to SpO2 range prescribed by local institutional policy. **Results:** 14 centers from 3 countries enrolled 78 infants with mean birth weight 863 g (SD 208 g) and mean gestational age 26 wk (SD 1.4 wk). Lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for median of 70 hours (25^{th}-75^{th} percentiles 67-71 hr) in each week. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25^{th}-75^{th} percentiles 91-97; range of study center medians 91-96). Centers ranged between 16-71% compliance with intended SpO2 range. Most noncompliance was above intended range. **Conclusions:** Compliance with intended SpO2 range during routine care varied substantially among participating centers, and was generally poor regardless of intended level. These data will assist quality improvement and education efforts, and will aid planning of prospective randomized trials examining level of oxygenation. **Disclosure:** Funded by the SPR Student Research Program; Fight for Sight/Prevent Blindness America; The Tufts-NEMC Research Fund; GCRC/Natl Center for Research Resources MO1-RR00054, and NEI K23 EY/HD00420. Oximeters provided by Masimo Corp.

Briefly describe the reason why the December deadline could not be met:
Study still in progress at December deadline, with only about 60% of enrollment achieved.

Person to whom all communication should be addressed: James Hagadorn, MD

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Boston, MA 02111 USA

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First Author is a member of: __ APS __SPR __APA __ASPHO __ASPN __LWPES

Conflict of Interest/Disclosure Statement/Approval of All Authors

Work submitted for presentation must include an acknowledgement of funding sources of commercial nature and/or consulting or holding of significant equity in a company that could be affected by the results of the study. The intent of this policy is not to prevent a speaker with a potential conflict of interest from making a presentation, it is merely intended that any potential conflict should be identified openly so that the listeners may form their own judgments about the presentation with the full disclosure of the facts. *Even if indicated elsewhere in the abstract, this must appear as the last sentence of the abstract and read "funded by..." and/or "equity in..." if pertinent.*

By emailing this electronic file, you verify that: You have the approval of all authors to submit this work for presentation; this work will not have been previously published in manuscript format; any animal studies conform with the "Guiding Principles in the Care and Use of Animals" of the American Physiological Society and any human experimentation has been conducted according to a protocol approved by the institutional committee on ethics of human investigation or if no such committee exists, that it conforms with the principles of the Declaration of Helsinki of the World Medical Association (CLINICAL RESEARCH 14:193, 1966)

Signature of First Author, attesting to the above: _____

Final Submission Steps:

- Attach this file to an email and send to: datwood@aps-spr.org
- Fax a copy of this form to PAS Late Breakers, 281-419-0082 along with your payment form

Questions? Call, 281-419-0052

Percent of time spent at each SpO2 value (data processed as of 12/02/2005)

Data included in tables and graphs (includes days on supplemental oxygen only)

Data included	High target (91-95)	Low target (85-89)	Total
Infants	78	88	166
Hours	55849	46824	102673

Percent of time spent at each actual SpO2 value, by treatment group

	High target (91-95)		Low target (85-89)	
SpO2	Percent	Cumulative	Percent	Cumulative
<70	1.12	1.12	2.06	2.06
70	0.14	1.26	0.25	2.31
71	0.17	1.43	0.29	2.60
72	0.19	1.62	0.34	2.94
73	0.22	1.84	0.39	3.33
74	0.26	2.10	0.45	3.77
75	0.30	2.40	0.52	4.29
76	0.36	2.76	0.60	4.89
77	0.43	3.19	0.71	5.60
78	0.51	3.70	0.84	6.44
79	0.61	4.31	1.01	7.45
80	0.73	5.05	1.20	8.65
81	0.89	5.93	1.45	10.11
82	1.07	7.01	1.77	11.88
83	1.30	8.30	2.17	14.05
84	0.00	8.30	1.87	15.92
84.25	0.00	8.30	0.76	16.68
84.5	0.00	8.30	0.81	17.49
84.75	0.00	8.30	0.87	18.36
85	0.00	8.30	2.11	20.47
85.5	7.60	15.90	0.00	20.47
86	0.00	15.90	3.94	24.41
87	0.00	15.90	3.72	28.13
88	2.19	18.10	3.33	31.47
89	2.48	20.57	3.47	34.93
90	3.43	24.00	4.57	39.51
91	5.52	29.52	6.75	46.25
92	7.32	36.84	7.59	53.84
93	8.93	45.77	0.00	53.84
94	10.24	56.00	0.00	53.84
94.5	0.00	56.00	30.69	84.53
95	7.23	63.23	0.00	84.53
95.25	2.92	66.16	0.00	84.53
95.5	2.87	69.03	0.00	84.53
95.75	2.85	71.88	0.00	84.53
96	6.68	78.56	0.00	84.53
97	8.42	86.98	6.14	90.67
98	6.25	93.22	4.51	95.18
99	3.90	97.13	2.75	97.93
100	2.88	100.00	2.07	100.00

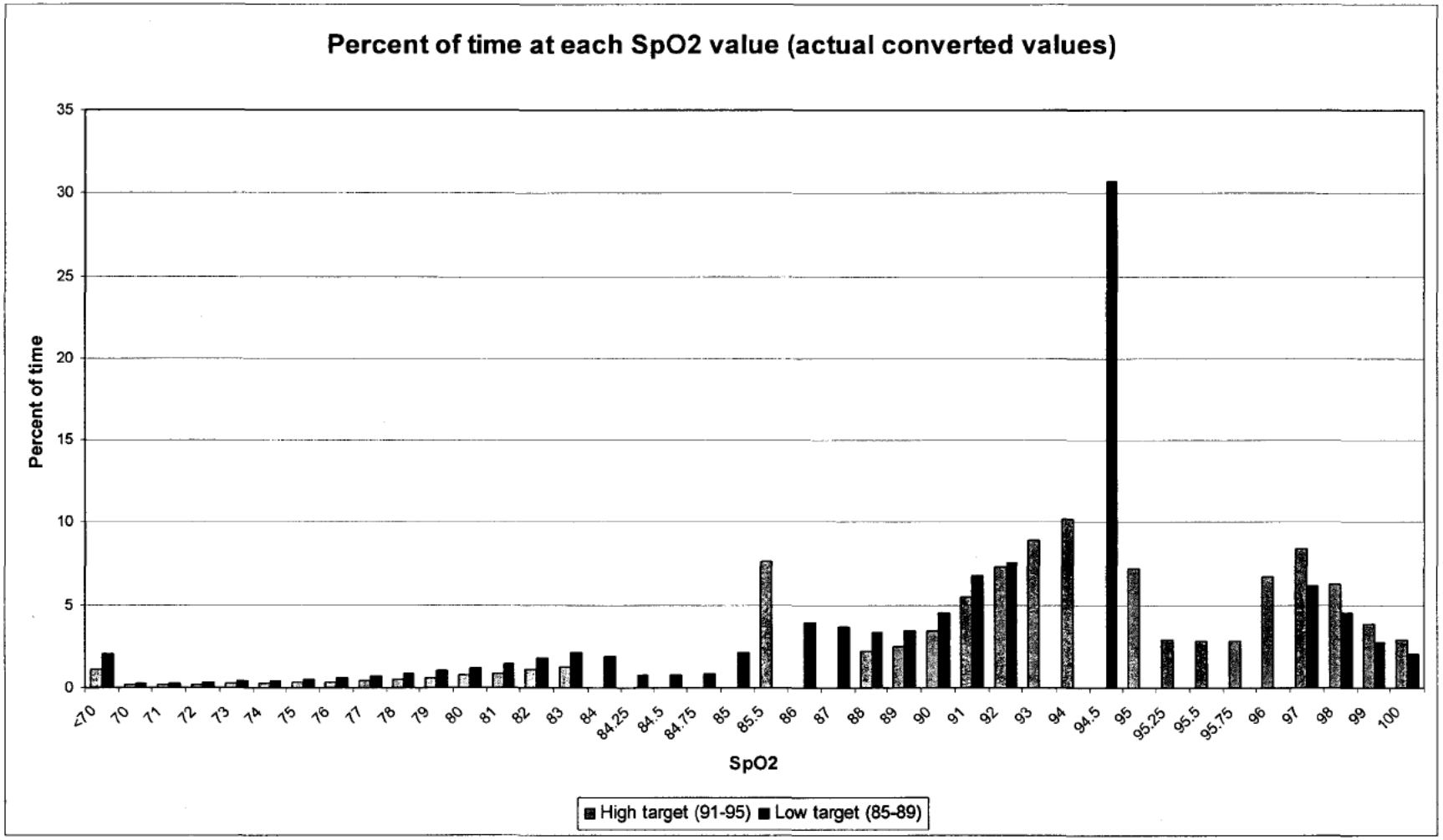
Median SpO2

	High target (91-95)	Low target (85-89)
Median	94	92

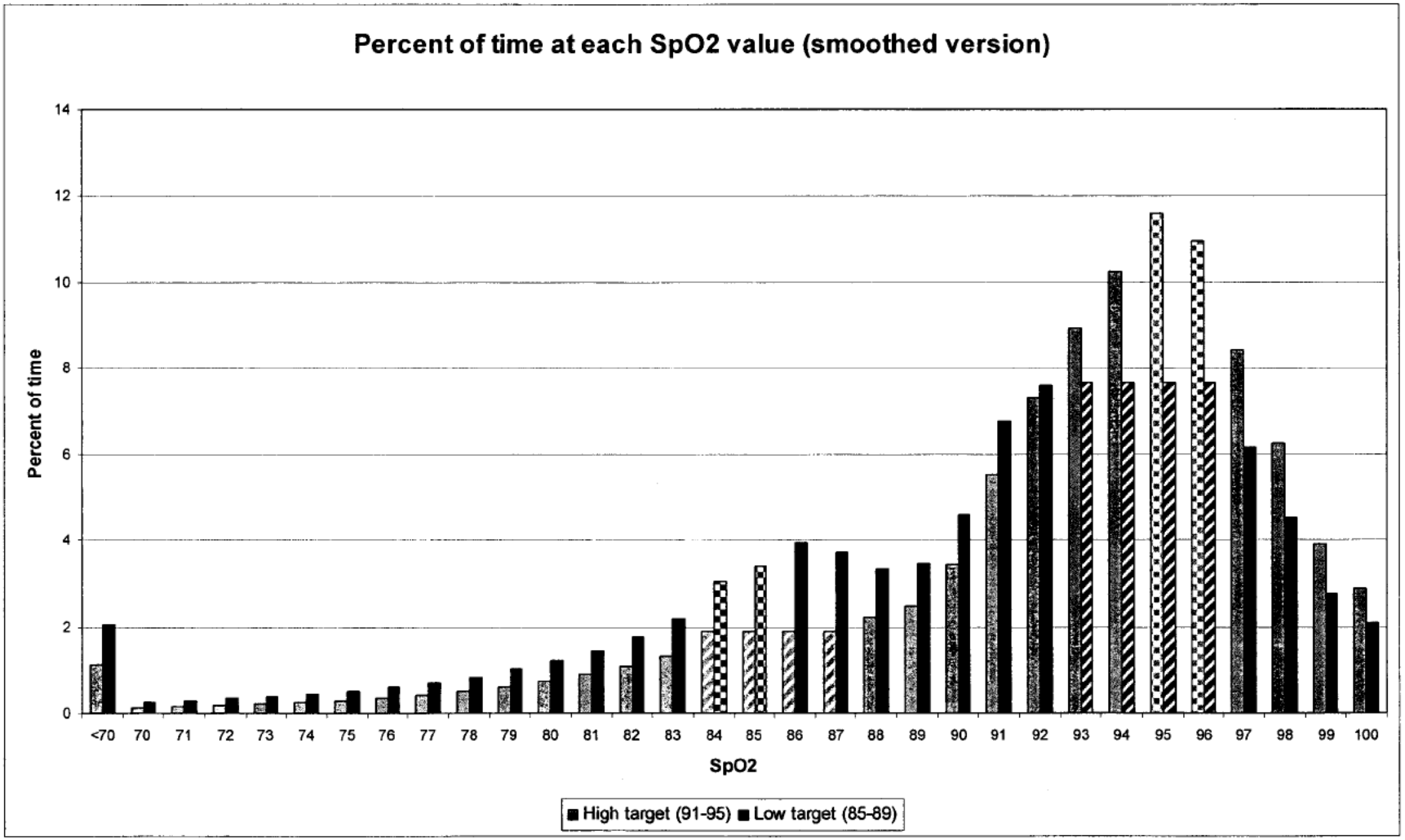
Percent of time of spent at SpO2 <84 and >96

Range	High target (91-95)	Low target (85-89)
<84	8.30	14.05
>96	21.44	15.47

The graph below displays each individual converted SpO2 value



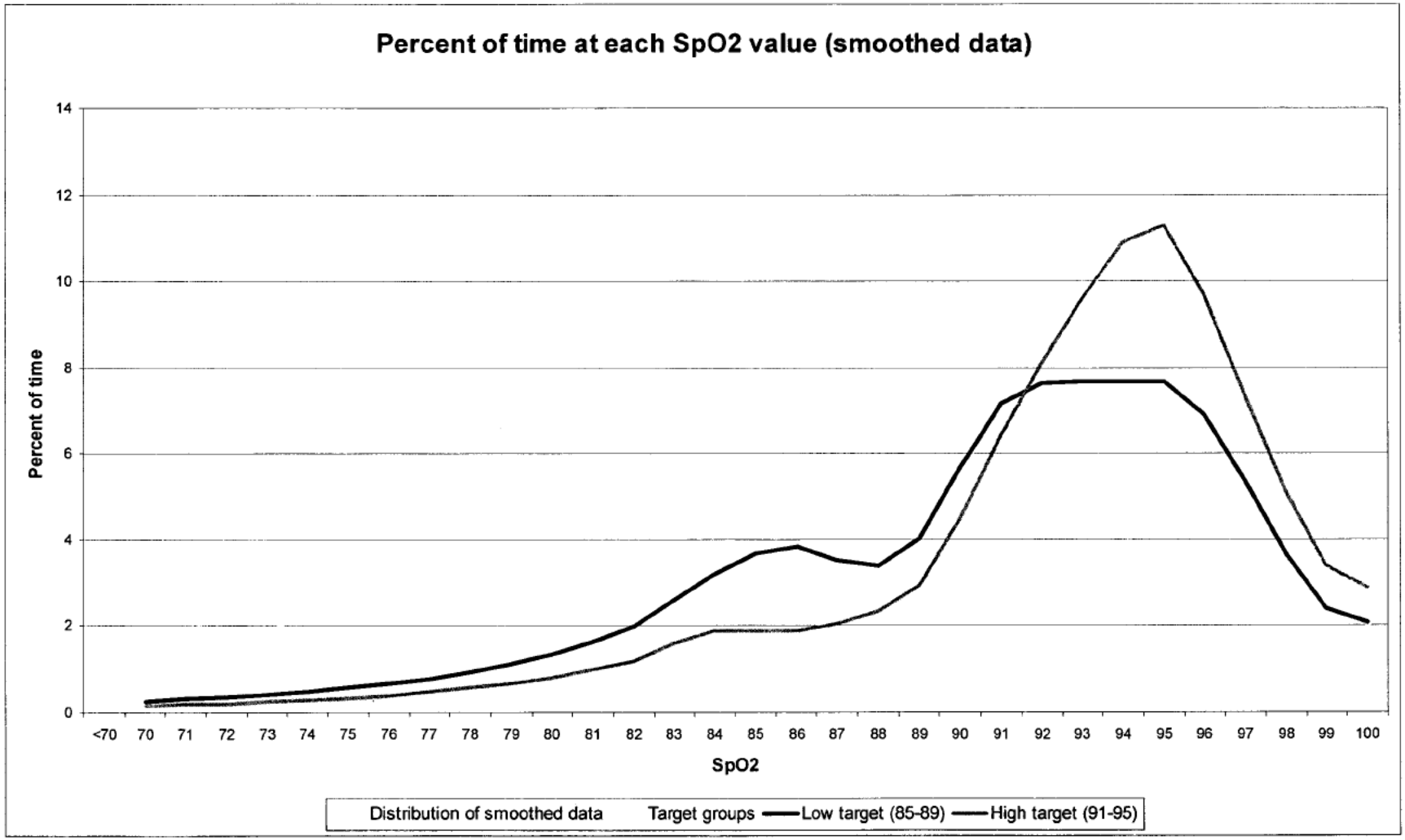
In the graph below, the converted SpO2 values have been smoothed to give a better idea of the distribution. Adjustments made to smooth the data are listed on the following page. Patterns are used to identify altered values.



Changes made to achieve smoothing

High target (91-95)	Pattern
Percent of time at converted value of 85.5 are spread evenly over 84-87	Blue diagonal stripes
Percent of time at 95 includes converted values of 95, 95.25 and half the percent of time at 95.5	Blue checked
Percent of time at 96 includes converted values of 96, 95.75 and half the percent of time at 95.5	Blue checked

Low target (85-89)	Pattern
Percent of time at converted value of 94.5 are spread evenly over 93-96	Burgundy diagonal stripes
Percent of time at 84 includes converted values of 84, 84.25 and half the percent of time at 84.5	Burgundy checked
Percent of time at 85 includes converted values of 85, 84.75 and half the percent of time at 84.5	Burgundy checked



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oxygen-Saturation Targets and Outcomes in Extremely Preterm Infants

Lisa Maree Askie, Ph.D., M.P.H., David John Henderson-Smart, Ph.D., M.B., B.S., Les Irwig, Ph.D., M.B., B.Ch., and Judy Margaret Simpson, Ph.D.

ABSTRACT

BACKGROUND

Physiological studies have shown that chronic hypoxemia may occur in preterm infants who require supplemental oxygen for extended periods and that this hypoxemia may contribute to poor growth and development. Anecdotal reports and uncontrolled observational studies have suggested that a higher oxygen-saturation range may be beneficial in terms of growth and development.

METHODS

We conducted a multicenter, double-blind, randomized, controlled trial involving 358 infants born at less than 30 weeks of gestation who remained dependent on supplemental oxygen at 32 weeks of postmenstrual age. They were randomly assigned to a target functional oxygen-saturation range of either 91 to 94 percent (standard-saturation group) or 95 to 98 percent (high-saturation group); this target was maintained for the duration of supplemental-oxygen therapy. The primary outcomes were growth and neurodevelopmental measures at a corrected age of 12 months.

RESULTS

There were no significant differences between the groups in weight, length, or head circumference at a corrected age of 12 months. The frequency of major developmental abnormalities also did not differ significantly between the standard-saturation group and the high-saturation group (24 percent and 23 percent, respectively, P=0.85). There were six deaths due to pulmonary causes in the high-saturation group and one such death in the standard-saturation group (P=0.12). The high-saturation group received oxygen for a longer period after randomization (median, 40 days vs. 18 days; P<0.001) and had a significantly higher rate of dependence on supplemental oxygen at 36 weeks of postmenstrual age and a significantly higher frequency of home-based oxygen therapy.

CONCLUSIONS

Targeting a higher oxygen-saturation range in extremely preterm infants who were dependent on supplemental oxygen conferred no significant benefit with respect to growth and development and resulted in an increased burden on health services.

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Improved survival of extremely preterm infants[1] has been associated with an increase in the incidence of chronic lung disease of infancy,[2] currently defined by a continued dependence on supplemental oxygen at 36 weeks of postmenstrual age.[3,4] This increased incidence has become a major clinical challenge, since chronic lung disease has serious health consequences, including poor growth,[5,6] neurologic impairment,[5,7] and pulmonary sequelae.[5,8] These and other factors may account for the higher reported health care costs for these infants than for infants who do not have chronic lung disease.[9]

Physiological studies have shown that infants with chronic lung disease (also known as bronchopulmonary dysplasia) have higher rates of oxygen consumption than infants without chronic lung disease,[10] as well as lower base-line oxygen-saturation levels, leading to more frequent episodes of desaturation.[11,12] In addition, observational studies have suggested that preterm infants who receive greater levels of oxygen supplementation, with either a longer duration of treatment or a higher target blood oxygen level, have improvements in sleep patterns,[13,14] growth, and neurodevelopmental outcomes.[15,16] Because of the uncontrolled nature of the studies, it is not known whether these associations are causal.

A policy of routine targeting of higher oxygen-saturation levels in preterm infants might result in some substantial burdens for the health care system and for parents, by increasing the duration of oxygen therapy in the hospital and the frequency of the need for home-based oxygen therapy. Despite some potential costs and the lack of evidence of long-term benefits, such policies are increasingly being implemented in clinical practice.[17,18] Data from randomized, controlled trials are lacking,[19,20] and the question of the most appropriate oxygen-saturation levels for preterm infants who require supplemental oxygen remains controversial.[21-23]

We conducted the randomized, multicenter Benefits of Oxygen Saturation Targeting (BOOST) trial to determine whether maintaining the oxygen saturation at a level higher than the standard range in extremely preterm infants with a long-term dependence on supplemental oxygen improves growth and neurodevelopmental outcomes. Secondary aims were to determine whether the higher oxygen-saturation levels had other beneficial or adverse physical or psychosocial effects on infants or parents.

METHODS

CRITERIA FOR ELIGIBILITY

Infants born at less than 30 weeks of gestational age (determined on the basis of the first day of the mother's last menstrual period, prenatal ultrasonography, or both or, if these data were not available, postnatal clinical assessment) who remained dependent on supplemental oxygen (delivered by any method and at any level) at 32 weeks of postmenstrual age were eligible for enrollment. Dependence on supplemental oxygen at 32 weeks of postmenstrual age, rather than 36 weeks, was used as a criterion for inclusion because it was current clinical practice to choose between the standard target range for oxygen saturation and a higher target range at this point in the infant's life. Criteria for exclusion before randomization included major congenital abnormalities, major surgery or a severe intracranial disorder diagnosed before 32 weeks of postmenstrual age, and a multiple birth in which three or more infants were eligible. The protocol allowed for infants from multiple gestations resulting in two eligible infants to be assigned to the same treatment.

The institutional ethics committees of the eight tertiary perinatal enrollment centers participating in the study approved the trial protocol, and written, informed consent was obtained from a parent or guardian of each eligible infant. Infants were enrolled between September 1996 and September 2000.

INTERVENTION AND BLINDING

Infants were randomly assigned to a target oxygen-saturation range of either 91 to 94 percent (standard-saturation group) or 95 to 98 percent (high-saturation group), as measured with a pulse oximeter (model N-3000, Nellcor) whose algorithm assesses functional oxygen saturation.[24] Randomization was stratified with the use of a dynamic balancing method[25] to ensure a balance of treatment-group assignments within each stratum defined according to hospital, singleton or multiple birth, and gestational age (22 to 27 weeks or 28 to 29 weeks). Central telephone randomization ensured concealment of the treatment-group assignments.

To make sure that the treatment-group assignments were not revealed, the infants who underwent randomization were assigned a specific study oximeter, which after the calculation of the infant's

oxygen-saturation level in the usual manner, was adjusted to display a value 2 percent higher than the actual saturation in infants in the standard-saturation group or 2 percent lower than the actual saturation in infants in the high-saturation group. Staff members and parents were then asked to target the range of 93 to 96 percent for the infant's oxygen saturation, so that they remained unaware of the actual ranges being targeted. Caregivers were aware that they were using adjusted oximeters and that they were participating in a trial, but they were not aware of the offset level of the individual oximeter. Double-blind targeting of the assigned saturation range was maintained for the duration of the infant's oxygen therapy either in the hospital (in both the enrollment center and other hospitals if necessary) or at home.

Dependence on supplemental oxygen was defined by the continuing need for oxygen therapy in order to maintain the double-blind target oxygen-saturation range of 93 to 96 percent, as measured by the assigned study oximeter. The frequency of monitoring of the saturation (continuous or intermittent), the settings for limits that were to trigger alarms, and the criteria for titrating the amount of ambient oxygen delivered or for ceasing delivery were determined by the attending clinicians and were not specified by the trial protocol.

ADHERENCE TO THE PROTOCOL

Compliance with the double-blind target oxygen-saturation range of 93 to 96 percent was assessed with the use of twice-weekly downloading of each infant's oxygen-saturation data, and a report on the distribution of the double-blind saturation levels was placed in the case notes. Clinicians and parents were allowed to violate the protocol either temporarily or permanently if they believed that the infant's condition warranted high-saturation oxygen therapy — for instance, because of serious intercurrent illness, as treatment for prethreshold retinopathy of prematurity, or during surgery.

PRIMARY OUTCOMES

The primary outcomes assessed at a corrected age of one year (the chronologic age plus the number of weeks of prematurity) included growth, in terms of the mean weight, the mean length, the mean head circumference, and the proportion of infants with a weight below the 10th percentile,[26] and the presence of a major developmental abnormality, defined as blindness, cerebral palsy, or a score on the revised Griffiths Mental Developmental Scales that was more than 2 SD below the mean (general quotient, <77).[27] Blindness was defined as a visual acuity in both eyes of less than 6/60.[28] Cerebral palsy was diagnosed if the child had nonprogressive motor impairment characterized by abnormal muscle tone and a decreased range or decreased control of movements, accompanied by neurologic signs.[29]

SECONDARY OUTCOMES

The secondary outcomes included the effect of the treatment-group assignment on the duration of oxygen therapy, the duration of assisted ventilation and of the hospital stay, and the frequency of home-based oxygen therapy. Parental stress and parent–infant interaction were assessed by means of validated scales (the Edinburgh Postnatal Depression Scale,[30] the Infant Temperament Questionnaire,[31] the Toddler Temperament Scale,[32] the Parenting Stress Index, Short Form,[33] and the Impact-on-Family Scale[34]). Retinopathy of prematurity was assessed by routine ophthalmic examinations at two-week intervals from enrollment until the resolution of retinopathy, with grading according to the International Classification of Retinopathy of Prematurity.[35] Reports by the parents on the use of health services and rehospitalizations during the first year of life were obtained through quarterly telephone contact by the research nurses, and rehospitalizations were confirmed through a review of the medical records. Causes of death were classified according to the codes of the *International Classification of Diseases, Ninth Revision*,[36] and confirmed on the basis of the hospital discharge summary, a postmortem examination report, a coroner's report, or a death certificate.

STATISTICAL ANALYSIS

All data analyses were performed according to the intention-to-treat principle. For continuous data, the treatment effect was calculated by subtracting the value for the standard-saturation group from the value for the high-saturation group, with results for normally distributed data presented as means ±SD and results for non–normally distributed data presented as medians with interquartile ranges. Differences between the two groups were assessed with the use of Student's t-test or the Mann–Whitney U test and are expressed as mean or median differences, respectively, with 95 percent confidence in-

tervals. For categorical data, the chi-square test was used, and the treatment effects are expressed as relative risks in the high-saturation group as compared with the standard-saturation group, with 95 percent confidence intervals. For analyses involving small numbers of events, Fisher's exact test was used, and exact confidence intervals were calculated for odds ratios, as approximate relative risks. All P values are two-sided and have not been adjusted for multiple testing or for correlation between the outcomes in siblings, since only 25 pairs of siblings were included (a total of 50 infants), representing 14 percent of the infants, and they were distributed approximately equally between the two groups.

The required sample size was calculated to ensure detection of clinically important effects on the primary outcomes: a reduction from the base-line estimate of 47 percent to 30 percent in the proportion of infants with a weight below the 10th percentile at a corrected age of 12 months, and a reduction in the frequency of major developmental abnormalities from 23 percent to 12 percent.[37] To achieve 80 percent power with a two-sided alpha level of 0.05 and a 1:1 ratio of infants in the two groups, approximately 150 infants were required in each group.

Table 1. Base-Line Characteristics of the Infants and Mothers.*

Characteristic	Standard-Saturation Group (N=178)	High-Saturation Group (N=180)
Birth weight — g	918±229	916±231
Gestational age at birth — wk	26.6±1.7	26.5±1.6
<28 Wk of gestation at birth — no. (%)	124 (70)	132 (73)
Male sex — no. (%)	92 (52)	97 (54)
Singleton birth — no. (%)	133 (75)	129 (72)
Born in tertiary care center — no. (%)	163 (92)	172 (96)
Surfactant treatment — no. (%)	138 (78)	137 (76)
Patent ductus arteriosus — no. (%)	94 (53)	91 (51)
Total duration of parenteral nutrition — days		
Median	13.5	13.0
Interquartile range	9.0–20.0	9.0–20.0
Antenatal corticosteroids — no. (%)	148 (83)	149 (83)
Score on the Edinburgh Postnatal Depression Scale†	10.7±5.7	10.0±5.3
Maternal educational level >high school — no. (%)	60 (34)	64 (36)
Maternal occupation score‡	4.5±1.4	4.6±1.3

* Plus–minus values are means ±SD.
† Scores range from 0 to 30, with higher scores indicating greater severity of depressive symptoms.[30]
‡ Data are the scores on Daniel's occupation scale[38]; scores range from 1 to 7, with lower scores indicating higher occupational prestige.

An independent safety monitoring committee, comprising a pediatric ophthalmologist, a neonatologist, and a pediatric respiratory physician–epidemiologist, all of whom were unaware of the treatment-group assignments, assessed adverse outcomes, including death, at five prespecified time points. The stopping rules were never breached.

RESULTS

PARTICIPANTS

Of the 703 infants who were eligible during the enrollment period, 158 met the criteria for exclusion before randomization. A total of 187 of the remaining 545 eligible infants were not enrolled (consent was not obtained for 122 infants, and the parent or guardian was not approached for 65 infants). There were 333 infants who underwent individual randomization, and an additional 25 eligible multiples were assigned to the same group as their sibling, for a total of 358 individual infants receiving one of the two treatments for whom outcomes were analyzed. A total of 178 infants were assigned to the standard-saturation group (target oxygen saturation, 91 to 94 percent) and 180 to the high-saturation group (target oxygen saturation, 95 to 98 percent). The two groups were well balanced in terms of the base-line characteristics of the infants and the mothers (Table 1). The intervention continued for a median of 17.5 days (interquartile range, 7.0 to 41.0) in the standard-saturation group and 40.0 days (interquartile range, 20.5 to 73.0) in the high-saturation group ($P<0.001$).

ADHERENCE TO THE PROTOCOL

Figure 1 shows the two distributions of the actual saturation levels. The median for each group was within the desired target range. Permitted protocol violations for open targeting of the oxygen saturation occurred relatively infrequently (on 54 occasions), generally for short periods (median, 7 days; interquartile range, 3 to 17), and the occurrences were equally distributed between the two groups.

PRIMARY OUTCOMES

The rate of ascertainment of primary outcomes was 93 percent in the standard-saturation group (165 of 178 infants) and 93 percent in the high-saturation group (168 of 180 infants). The median age at the assessment of the primary outcomes did not differ between the two groups (a corrected age of 12.1 months [interquartile range, 11.8 to 12.7] in the standard-saturation group and a corrected age of

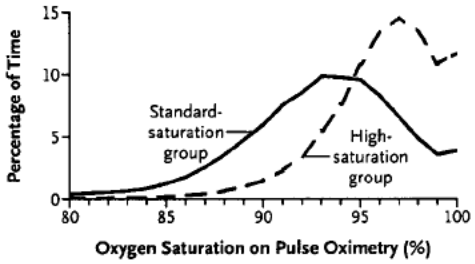

Figure 1. Smoothed Frequency Distribution of Actual Oxygen-Saturation Values on Pulse Oximetry during Oxygen Therapy after Randomization.

The saturation values were sampled every 10 seconds during intermittent downloads performed approximately twice weekly and lasting 8 to 24 hours each. The median oxygen saturation was 93 percent in the standard-saturation group (interquartile range, 90 to 96) and 97 percent in the high-saturation group (interquartile range, 94 to 98).

12.2 months [interquartile range, 11.9 to 12.9] in the high-saturation group).

There were no significant differences between the two groups in the mean weight, length, or head circumference at 38 weeks of postmenstrual age (Table 2). In addition, at a corrected age of 12 months, there were no significant differences in the measurements of weight, length, or head circumference; the proportion of infants who were small for their age; or the proportion of infants with a major developmental abnormality (Table 2). Our data also showed no significant difference between the two groups in the frequency of developmental scores that were more than 1 SD but less than 2 SD below the mean (relative risk associated with the higher oxygen-saturation target, 1.08; 95 percent confidence interval, 0.69 to 1.69; P=0.70). When the primary outcomes were examined in the subgroup of 256 infants born before 28 weeks of gestation, the differences between the two treatment groups remained nonsignificant and were similar

Table 2. Measures of Growth and Development.*

Outcome	Standard-Saturation Group	High-Saturation Group	Mean Difference (95% CI)	Relative Risk or Odds Ratio (95% CI)†	P Value
38 Wk of postmenstrual age					
Weight — g	2345±429	2369±428	24.0 (−66 to 113)		0.60
Length — cm	44.2±3.2	44.2±3.2	0.0 (−0.6 to 0.7)		1.00
Head circumference — cm	33.1±2.2	32.9±1.9	−0.2 (−0.7 to 0.2)		0.26
12 Mo of corrected age					
Weight — kg	9.10±1.5	9.25±1.6	0.15 (−0.2 to 0.5)		0.33
Length — cm	74.0±3.9	74.1±4.1	0.1 (−0.8 to 1.0)		0.77
Head circumference — cm	46.3±2.0	46.3±1.9	0.0 (−0.4 to 0.4)		1.00
Weight below 10th percentile — no./total no. (%)	61/165 (37)	55/168 (33)		0.89 (0.66 to 1.19)	0.42
Length below 10th percentile — no./total no. (%)	42/162 (26)	41/164 (25)		0.96 (0.67 to 1.40)	0.85
Head circumference below 3rd percentile — no./total no. (%)	5/165 (3)	8/165 (5)		1.63 (0.46 to 6.47)	0.57
Major developmental abnormality — no./total no. (%)‡	40/166 (24)	39/168 (23)		0.96 (0.66 to 1.42)	0.85

* Plus–minus values are means ±SD. Denominators are the numbers of infants for whom growth measures or major developmental abnormalities could be assessed at 12 months of corrected age. CI denotes confidence interval.

† The value for a head circumference below the 3rd percentile is an odds ratio; other values are relative risks.

‡ Major developmental abnormalities were blindness, cerebral palsy, or a general quotient on the revised Griffiths Mental Developmental Scales that was more than 2 SD below the mean.

in magnitude to those in the whole cohort (data not shown).

SECONDARY OUTCOMES

The proportion of infants who were still dependent on supplemental oxygen at 36 weeks of postmenstrual age was 46 percent in the standard-saturation group and 64 percent in the high-saturation group (P<0.001) (Table 3). Similarly, the proportion of infants requiring home-based oxygen therapy was significantly lower in the standard-saturation group than in the high-saturation group (17 percent vs. 30 percent, P=0.004) (Table 3). The duration of oxygen supplementation was significantly higher in the high-saturation group: the postmenstrual age at the cessation of oxygen therapy was 35.4 weeks in the standard-saturation group and 37.9 weeks in the high-saturation group (P<0.001) (Table 3). There were no significant differences between the two groups in the median total duration of assisted ven-

Table 3. Rates of Adverse Outcomes among the Infants.*

Outcome	Standard-Saturation Group (N=178)	High-Saturation Group (N=180)	Relative Risk or Odds Ratio (95% CI)†	Median Difference (95% CI)	P Value
Dependence on supplemental oxygen at 36 wk of postmenstrual age — no. (%)	82 (46)	116 (64)	1.40 (1.15 to 1.70)		<0.001
Home-based oxygen therapy — no. (%)	30 (17)	54 (30)	1.78 (1.20 to 2.64)		0.004
Duration of oxygen therapy after randomization — days				17 (12 to 23)	<0.001
Median	17.5	40.0			
Interquartile range	7.0 to 41.0	20.5 to 73.0			
Postmenstrual age at cessation of oxygen therapy — wk				2.3 (1.3 to 3.3)	<0.001
Median	35.4	37.9			
Interquartile range	33.4 to 39.7	35.4 to 45.1			
Duration of assisted ventilation after randomization — days				0 (−4 to 4)	0.95
Median	14.0	14.0			
Interquartile range	7.0 to 28.0	6.0 to 35.0			
Postnatal corticosteroids — no. (%)	89 (50)	104 (58)	1.16 (0.95 to 1.40)		0.14
Diuretics for chronic lung disease — no. (%)	78 (44)	93 (52)	1.18 (0.95 to 1.47)		0.14
Length of hospital stay after randomization — days				2 (−1 to 5)	0.24
Median	50.0	50.0			
Interquartile range	39.0 to 60.0	42.0 to 61.5			
Postmenstrual age at discharge from hospital — wk				0.29 (−0.14 to 0.86)	0.15
Median	39.1	39.1			
Interquartile range	37.4 to 40.4	37.9 to 40.8			
Postmenstrual age at time of fully oral feeding — wk				0.00 (−0.43 to 0.43)	0.91
Median	37.7	37.7			
Interquartile range	36.6 to 39.0	36.4 to 38.9			
Worst retinopathy of prematurity — no. (%)					
<Stage 3	150 (84)	158 (88)	1.04 (0.96 to 1.13)		0.34
Stage 3 or 4	28 (16)	22 (12)	0.78 (0.46 to 1.31)		0.34
Ablative retinal surgery for severe retinopathy of prematurity — no. (%)‡	20 (11)	11 (6)	0.54 (0.27 to 1.10)		0.09
Death (after randomization) — no. (%)	5 (3)	9 (5)	1.82 (0.53 to 7.05)		0.41

* CI denotes confidence interval.
† The value for death is an odds ratio; all other values are relative risks.
‡ Data are for infants who underwent cryotherapy or laser therapy for threshold retinopathy of prematurity, usually stage 3 with dilatation of the posterior retinal vessels (referred to as "plus" disease).

tilation after randomization, the rate of use of postnatal corticosteroids or diuretics, the length of the hospital stay after randomization, the postmenstrual age at discharge, or the time before the infant was able to be fed entirely orally (Table 3).

There were no significant differences between the groups in the rates of retinopathy of prematurity of any stage or in the frequency of the need for ablative retinal surgery (in 20 of 178 infants in the standard-saturation group [11 percent] and 11 of 180 infants in the high-saturation group [6 percent], P=0.09) (Table 3). All the infants who underwent ablative retinal surgery were born before 28 weeks of gestation, and all but one of these infants retained vision in at least one eye. The rate of ablative retinal surgery among infants born before 28 weeks of gestation was 16 percent (20 of 124 infants) in the standard-saturation group and 8 percent (11 of 132 infants) in the high-saturation group (relative risk, 0.52; 95 percent confidence interval, 0.26 to 1.03; P=0.06).

There was no significant difference between the two groups in the number of infants who died: five infants in the standard-saturation group and nine in the high-saturation group (Table 3). Of these deaths, one in the standard-saturation group was due to pulmonary causes, as compared with six in the high-saturation group (P=0.12). The number of infants who were rehospitalized and the number of health service visits per infant during the first year of life did not differ significantly according to the treatment group (Table 4). There were also no significant differences between the two groups in the measures of maternal postnatal depression, infant or toddler temperament, parental stress, or effects on the family (Table 4). Follow-up rates for these tests ranged from 71 to 77 percent.

DISCUSSION

Our double-blind, randomized trial showed no evidence that the targeting of a functional oxygen-saturation range of 95 to 98 percent rather than a range of 91 to 94 percent had a beneficial effect on growth or development in preterm infants with a long-term dependence on supplemental oxygen. The targeting of higher oxygen-saturation levels resulted in a 40 percent increase in the proportion of infants who were still receiving oxygen therapy at 36 weeks of postmenstrual age and a 78 percent increase in the

Table 4. Use of Health Services in the First Year of Life and Psychosocial Measures in Parents and Infants.*

Outcome	Standard-Saturation Group	High-Saturation Group	Relative Risk (95% CI)	Difference between Groups (95% CI)†	P Value
Infant rehospitalized — no./total no. (%)	82/171 (48)	92/170 (54)	1.13 (0.92 to 1.39)		0.34
No. of health service visits/infant				3.8 (−0.8 to 8.5)	0.11
Median	27.5	31.3			
Interquartile range	25.1 to 30.4	27.3 to 34.8			
Scores on psychosocial measures‡					
Edinburgh Postnatal Depression Scale (mother)	5.9±5.1	6.5±4.8		0.6 (−0.6 to 1.8)	0.32
Infant Temperament Scale	2.3±0.7	2.4±0.7		0.1 (0.0 to 0.3)	0.06
Toddler Temperament Scale	3.2±0.6	3.1±0.6		−0.1 (−0.2 to 0.1)	0.59
Parenting Stress Index, Short Form	71.7±20.6	72.9±21.1		1.2 (−3.9 to 6.3)	0.65
Impact-on-Family Scale	40.0±11.0	39.8±11.7		−0.2 (−3.0 to 2.6)	0.89

* Plus–minus values are means ±SD. Scores on the Edinburgh Postnatal Depression Scale[30] range from 0 to 30, with higher scores indicating a greater severity of depressive symptoms. Scores on the Infant Temperament Scale[31] range from 1 to 6, with a mean (±SD) of 2.5±0.64; higher scores indicate a more difficult temperament. Scores on the Toddler Temperament Scale[32] range from 1 to 6, with a mean of 3.46±0.62; higher scores indicate a more difficult temperament. Scores on the Parenting Stress Index, Short Form,[33] range from 32 to 160, with a median of 69 (interquartile range, 61 to 79); higher scores indicate greater parental stress. Scores on the Impact-on-Family Scale[34] range from 19 to 76, with a mean of 46.2±7.6; higher scores indicate increased effects on the family. CI denotes confidence interval.

† The mean difference is shown for scores on psychosocial measures; the median difference is shown for health service visits.

‡ The score on the Infant Temperament Scale was obtained at 4 months of corrected age; scores on the other measures were obtained at 12 months of corrected age.

proportion receiving supplemental oxygen after discharge. Hence, one could expect one additional case of home-based oxygen therapy for every eight infants treated if higher target ranges for the oxygen saturation were used routinely.

The finding that oxygen therapy was required for a longer period in the high-saturation group might simply be explained by the fact that a higher target saturation had to be reached for oxygen therapy to be discontinued. However, a higher target oxygen saturation may also be associated with potential pulmonary toxicity. The unexpected finding of excess deaths from pulmonary causes among infants in the high-saturation group — albeit not statistically significant — accords with the findings of the only other trial in which preterm infants were randomly assigned to different target oxygen-saturation ranges, the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial.[39] That trial showed an increased rate of adverse pulmonary sequelae (although not an increased rate of death due to pulmonary causes) among preterm infants with prethreshold retinopathy of prematurity when a higher oxygen-saturation range was targeted.

Oxygen toxicity, particularly in preterm infants, can inhibit lung healing and contribute to ongoing lung injury.[40] In our trial, infants who were still dependent on supplemental oxygen at 36 weeks of postmenstrual age or before discharge did not routinely have oxygen-saturation data collected after a room-air breathing test, and we do not have information on the proportion of infants in the high-saturation group who would not have required oxygen had their oxygen-saturation target been lower. Thus, the cause of the greater oxygen requirement in the high-saturation group remains uncertain.

Although our trial did not have the statistical power to detect differences in secondary eye-related outcomes, the effect of different target oxygen-saturation ranges on retinopathy of prematurity is of interest, since infants were randomly assigned to the different treatments at 32 weeks of postmenstrual age, before threshold retinopathy of prematurity usually develops. The results of both the STOP-ROP trial and our trial suggest the possibility that the need for ophthalmic intervention may be reduced when a higher oxygen-saturation range is targeted in a subgroup of extremely preterm infants with more severe eye disease. However, the differences between the treatment groups were not significant at the $P<0.05$ level in our subgroup analysis, and this hypothesis requires confirmation in larger studies.

Our trial addressed only the question of the effects of two different target oxygen-saturation ranges in preterm infants who remained dependent on supplemental oxygen after 32 weeks of postmenstrual age. Hence, these results should not be extrapolated to practice recommendations for preterm infants at earlier postmenstrual ages. The question of the most appropriate oxygen-saturation range for preterm infants treated sooner after birth can be answered only in the context of further large, well-designed, randomized trials with good long-term follow-up.[21]

A possible limitation of the study is that the duration of follow-up may not have been sufficiently long to allow us to detect other clinically important outcomes, such as minor disabilities that may become manifest later in childhood. We found no significant difference in the rates of developmental scores that were more than 1 SD but less than 2 SD below the mean — an outcome that may be a surrogate for later minor disability.[41]

The results of this randomized trial contradict observational reports suggesting that there are benefits of the routine targeting of higher oxygen-saturation levels in preterm infants with a long-term dependence on supplemental oxygen.[13-16] We found no evidence of beneficial effects of higher oxygen-saturation levels on growth or neurodevelopmental outcomes in these infants, but we did find an increased burden on health services.

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Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), A Randomized, Controlled Trial. I: Primary Outcomes

The STOP-ROP Multicenter Study Group

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Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), A Randomized, Controlled Trial. I: Primary Outcomes

The STOP-ROP Multicenter Study Group*

ABSTRACT. *Objective.* To determine the efficacy and safety of supplemental therapeutic oxygen for infants with prethreshold retinopathy of prematurity (ROP) to reduce the probability of progression to threshold ROP and the need for peripheral retinal ablation.

Methods. Premature infants with confirmed prethreshold ROP in at least 1 eye and median pulse oximetry <94% saturation were randomized to a conventional oxygen arm with pulse oximetry targeted at 89% to 94% saturation or a supplemental arm with pulse oximetry targeted at 96% to 99% saturation, for at least 2 weeks, and until both eyes were at study endpoints. Certified examiners masked to treatment assignment conducted weekly eye examinations until each study eye reached ophthalmic endpoint. An adverse ophthalmic endpoint for an infant was defined as reaching threshold criteria for laser or cryotherapy in at least 1 study eye. A favorable ophthalmic endpoint was regression of the ROP into zone III for at least 2 consecutive weekly examinations or full retinal vascularization. At 3 months after the due date of the infant, ophthalmic findings, pulmonary status, growth, and interim illnesses were again recorded.

Results. Six hundred forty-nine infants (325 conventional and 324 supplemental) were enrolled from 30 centers over 5 years. Five hundred ninety-seven (92.0%) infants attained known ophthalmic endpoints, and 600 (92%) completed the ophthalmic 3-month assessment. The rate of progression to threshold in at least 1 eye was 48% in the conventional arm and 41% in the supplemental arm. After adjustment for baseline ROP severity stratum, plus disease, race, and gestational age, the odds ratio (supplemental vs conventional) for progression was .72 (95% confidence interval: .52, 1.01). Final structural status of all study eyes at 3 months of corrected age showed similar rates of severe sequelae in both treatment arms: retinal detachments or folds (4.4% conventional vs 4.1% supplemental), and macular ectopia (3.9% conventional vs 3.9% supplemental). Within the prespecified ROP severity strata, ROP progression rates were lower with supplemental oxygen than with conventional oxygen, but the differences were not statistically significant. A post hoc subgroup analysis of plus disease (dilated and tortuous vessels in at least 2 quadrants of the posterior pole) suggested that infants without plus disease may be more responsive to supplemental therapy (46% progression in the conventional arm vs 32% in the supplemental arm) than infants with plus disease (52% progression in conventional vs 57% in supplemental).

Pneumonia and/or exacerbations of chronic lung disease occurred in more infants in the supplemental arm (8.5% conventional vs 13.2% supplemental). Also, at 50 weeks of postmenstrual age, fewer conventional than supplemental infants remained hospitalized (6.8% vs 12.7%), on oxygen (37.0% vs 46.8%), and on diuretics (24.4% vs 35.8%). Growth and developmental milestones did not differ between the 2 arms.

Conclusions. Use of supplemental oxygen at pulse oximetry saturations of 96% to 99% did not cause additional progression of prethreshold ROP but also did not significantly reduce the number of infants requiring peripheral ablative surgery. A subgroup analysis suggested a benefit of supplemental oxygen among infants who have prethreshold ROP without plus disease, but this finding requires additional study. Supplemental oxygen increased the risk of adverse pulmonary events including pneumonia and/or exacerbations of chronic lung disease and the need for oxygen, diuretics, and hospitalization at 3 months of corrected age. Although the relative risk/benefit of supplemental oxygen for each infant must be individually considered, clinicians need no longer be concerned that supplemental oxygen, as used in this study, will exacerbate active prethreshold ROP. *Pediatrics* 2000;105:295–310; *retinopathy of prematurity, oxygen therapy, visual loss, oxygen toxicity, prematurity, neonatal outcomes, bronchopulmonary dysplasia.*

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ABBREVIATIONS. ROP, retinopathy of prematurity; CRYO-ROP,

cryotherapy for ROP; STOP-ROP, Supplemental Therapeutic Oxygen for Prethreshold ROP; PMA, postmenstrual age; SES, socioeconomic status; CLD, chronic lung disease; CPAP, continuous positive airway pressure; OR, odds ratio; CI, confidence interval.

Retinopathy of prematurity (ROP) is a neovascular retinal disorder that develops in 84% of premature survivors born at <28 weeks' gestation. Fortunately, ROP resolves in most cases (80%) without visual loss from retinal detachments or scars.[1,2] The multicenter study of cryotherapy for ROP (CRYO-ROP) study showed that, when the disorder progresses, ablation of the avascular peripheral retina with cryotherapy reduced the incidence of retinal detachment from 51% to 31%.[3] Peripheral retinal ablation, now usually by laser therapy, has become standard treatment for advanced ROP.[4–7] However, this therapy is not always successful in halting the progression of ROP, and the long-term complications of extensive ablation of the developing peripheral retina beyond 5 years of age[7] are as yet unknown.

In 1948, Michaelson[8] proposed that a gradually increasing oxygen deficit of the oxygen-consuming retina during normal differentiation causes release of an angiogenic growth factor. Based on this supposition, therapeutic administration of supplemental oxygen to relieve the putative hypoxic stimulus for retinal neovascularization has been considered. In the 1950s, Szewczyk[9] and Bedrossian et al[10,11] first reported the use of supplemental oxygen to treat the neovascularization in ROP. This approach was abandoned after the 1956 Cooperative Study of Retrolental Fibroplasia demonstrated that prolonged (4 weeks) administration of 50% oxygen caused increased rates of ROP and vision loss.[12] But the concept of an hypoxic stimulus for retinal neovascularization remained biologically plausible and eventually regained scientific interest and attention.

Case–control studies revealed that infants who develop severe ROP, compared with infants of similar gestation and birth weight who do not have ROP, have hospital courses characterized by more complex medical problems, prolonged oxygen requirements, lower overall arterial oxygenation levels, and more episodes of fluctuating blood oxygen levels.[13–15] In contrast to healthy neonates breathing room air, whose arterial oxygen levels are similar to those of adults (95–100 mm Hg [13 pKa]), the recommended arterial concentrations for premature infants receiving oxygen are 50 to 80 mm Hg (6.6–10.6 kPa).[16] This relative hypoxia in premature infants raised the possibility that supplemental oxygen might be used to improve retinal oxygenation and down-regulate retinal neovascularization. Tests of the effects of such oxygen supplementation in animal models of ROP supported this hypothesis,[17,18] and a reported benefit of supplemental oxygen in a clinical case series[19] provided additional support for systematically testing the hypothesis in premature infants with ROP. We report the primary results from the Supplemental Therapeutic Oxygen for Prethreshold ROP (STOP-ROP) study, which was designed to test the hypothesis that supplemental oxygen, given to attain a pulse oximetry range of 96% to 99% saturation, would reduce by one third the proportion of infants with at least 1 eye progressing from moderate ROP (prethreshold) to threshold ROP requiring peripheral ablative surgery, without unacceptable side effects.[20]

METHODS

Study Design

The study design was a randomized trial comparing the effects of 2 oxygenation strategies on the progression of ROP: conventional oxygenation at a pulse oximetry target of 89% to 94% versus supplemental oxygen to achieve a pulse oximetry target range of 96% to 99%.[21] From February 1994 to March 1999, eligible patients from 30 centers were typically enrolled by telephone call to the central coordinating center (64%) after confirmation of eligibility and signed informed consent by parents or legal guardians. Random assignments were generated by the coordinating center using the Wei-Lachin Urn Scheme[22] and were stratified by center and by 2 levels of baseline ROP severity. When the coordinating center was not available, study centers used sequentially numbered, sealed envelopes provided in advance by the coordinating center to obtain treatment assignments, and submitted appropriate documentation to the coordinating center. An infant was assigned to the severe ROP stratum A whenever either study eye had 1 or more clock hours of any stage ROP in zone I, or when the fellow eye was already at threshold or worse ROP (see Table 1), thereby eliminating that eye as a study eye. The remaining infants fell in the less severe ROP stratum B with zone II prethreshold ROP in both eyes or in the second eye at less than prethreshold ROP. Family, bedside nurses, and attending neonatologists knew the treatment assignment, but the study-certified ophthalmologists who assessed eligibility, progression of the ROP, and study end-

TABLE 1. Definitions of ROP Severity Categories for STOP-ROP

Threshold ROP*	
Zone II	Presence of posterior pole dilation/tortuosity in at least 2 posterior pole quadrants (plus disease), and stage 3 ROP for at least 5 contiguous clock h or 8 composite clock h
Zone I	ROP (any stage) with posterior pole dilation/tortuosity in at least 2 posterior pole quadrants (plus disease), or stage 3 ROP, with or without plus disease
Beyond threshold	Stage 4 ROP, stage 5 ROP, or massive vitreal hemorrhage obscuring the view of the fundus
Prethreshold ROP	
Zone II	Any number of clock hours of stage 3 ROP, less than threshold severity, or any stage 2 ROP with at least 2 quadrants of posterior pole dilation/tortuosity disease (plus disease)
Zone I	Any ROP less than threshold severity

Stages and zones based on the international classification of ROP.[24]

* The definition of threshold ROP differs somewhat from that used in the CRYO-ROP study[4] in 2 ways: 1) In the CRYO-ROP study, "plus disease" was a global assessment of the posterior pole and was not determined according to number of quadrants involved, and 2) in the CRYO-ROP study, the definition of threshold was the same for both zone I and zone II and is the same as stated for zone II above (except for the number of quadrants of posterior pole dilation/tortuosity, as described in note 1). In STOP-ROP, a less stringent definition of threshold in zone I was used to accommodate the clinical judgment of a majority of the participating ophthalmologists that earlier treatment was needed to improve the poor outcomes of zone I threshold ROP.

points remained masked to treatment assignment throughout the study.

The primary endpoint of this study of systemic oxygen therapy was based on the infant, ie, progression of at least 1 study eye of an infant to threshold ROP (Table 1). Infants had only 1 study eye if the fellow eye was already at threshold or worse than threshold ROP at enrollment. Otherwise, they had 2 study eyes; even a fellow eye at less than prethreshold severity was considered a study eye, because it was going to be exposed to the assigned treatment and could progress to threshold ROP. Secondary endpoints included ophthalmic status at 3 months after due date, infant growth rates, developmental screening, and adverse medical events. The protocol was reviewed and approved by the institutional review board at each participating site before initiation of recruitment at that site.

Eligibility Criteria

Premature infants were screened for ROP, according to local guidelines consistent with the 1992 recommendations of the American Academy of Pediatrics,[16] at 71 hospitals affiliated with 30 certified participating centers throughout the United States. Infants with prethreshold ROP in at least 1 eye (Table 1) were registered as potentially eligible for the study and monitored for a minimum of 4 hours with continuous pulse oximetry. Registered candidates were excluded as ineligible whenever their median pulse oximetry was greater than 94% saturation while breathing room air or they had lethal anomalies or congenital anomalies of the eye. The family or guardian of eligible infants was approached for consent if the attending neonatologist agreed that randomization to either oxygen saturation target range could be achieved and would be medically safe, and that the infant's caretaker would be able to comply with the follow-up appointments. The diagnosis of prethreshold ROP in at least 1 eye then had to be confirmed independently by a second examiner to qualify for randomization. At least 1 of the 2 examiners had to be certified by the STOP-ROP study; usually both were.

Intervention

Although randomization and initiation of treatment within 24 hours of the diagnosis of prethreshold ROP was the goal, later enrollment was permitted as long as at least 1 eye was verified as remaining at prethreshold within the preceding 48 hours. The treatment assignment was for the infant to be placed on continuous pulse oximetry monitoring and to maintain oxygen saturation, as much as possible, in the target range of either 89% to 94% (conventional) or 96% to 99% (supplemental). Ohmeda 3740 pulse oximeters and laptop computers with software to monitor, record, and report trends in oxygen saturation were provided by the study for each infant. The Ohmeda 3740 pulse oximeter is calibrated at the factory to display a saturation lower by 1.6 saturation points, compared with other commercial oximeters, to correct for assumed carboxyhemaglobin and methemaglobin levels. Oximeters provided continuous data to a laptop computer that displayed real-time oxygen saturation summary graphs and tables updated every 20 seconds. The percent time in the assigned target range over varying time periods was displayed (Fig 1). Whenever the oxygen saturation was out of the target range for >10 of the previous 20 minutes and the saturation was currently out of range, the computer produced a unique alarm. The alarm limits on the oximeter itself were set according to the each hospital's usual policy. Using this continuous feedback, the bedside nurse or family could readily make necessary adjustments to the oxygen environment to maximize the time spent in the assigned target range. Pulse oximetry values were recorded to a computer disk every 40 seconds during the weeks the infant was on study equipment.

Study saturation targets continued for a minimum of 2 weeks, even if ophthalmic endpoints were reached in both eyes sooner. After those 2 weeks, treatment assignment and equipment were stopped after both eyes reached ophthalmic endpoints. Brief periods off equipment were allowed for procedures or baths. Occasionally an infant was ready for discharge home before reaching study endpoint in both eyes. The parents or guardians were then trained to use the study oximeter and computer to permit the assigned treatment to be continued, recorded, and completed at home.

Outcome Variables

Study-certified ophthalmologists and study center coordinators examined enrolled infants weekly until both eyes reached oph-

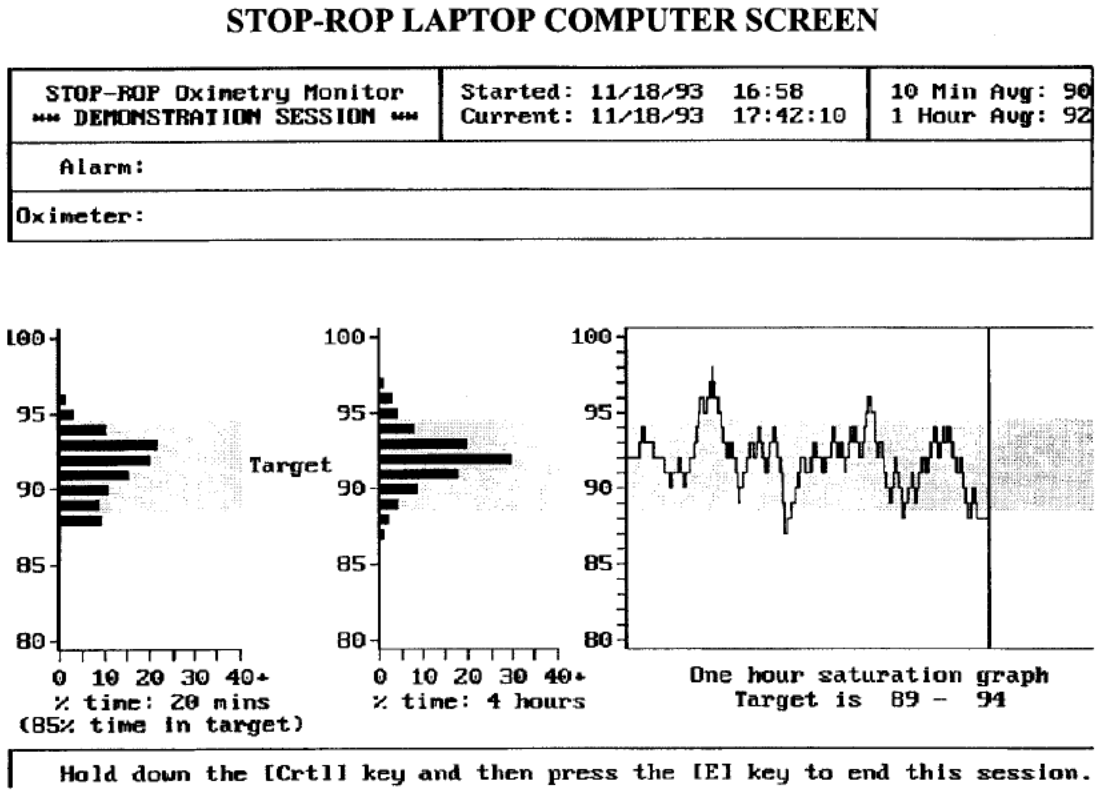

Fig 1. Computer screen format. Frequency distributions and oximetry strip chart information provided continuously at the bedside for nursing management of the pulse oximetry study targets. In this sample, the infant is assigned to the conventional arm (89%–94% saturation), the area highlighted in gray.

thalmic endpoints and again at 3 months' corrected age (that is, 3 months past the term due date of 40 weeks' postmenstrual age [PMA]). The computers and oximeters were covered during examinations to maintain masking of the ophthalmologists. To standardize diagnoses, all ophthalmologists were certified in the completion of study data forms. If they had not been previously certified during the acute phase of the CRYO-ROP or Light Reduction-ROP studies,[23] their use of the international classification of ROP[24] was certified by study headquarters through a series of dual examinations of infants with ROP. Standard fundus photographs of degrees of severity of posterior pole dilation/tortuosity were provided to each center for use at the bedside to promote uniformity of the diagnosis (Fig 2). For the STOP-ROP study, plus disease was defined as "at least 2 quadrants of dilation and tortuosity of the posterior pole vessels." Study personnel completed annual recertification throughout the study.

An adverse ophthalmic endpoint was defined as progression to threshold ROP (or worse), diagnosed by 1 study-certified ophthalmologist and confirmed independently by a second study-certified ophthalmologist. Eyes confirmed to have reached threshold ROP were referred for possible cryotherapy or laser therapy. The definition of threshold ROP (Table 1) in zone II was the same as that used by the CRYO-ROP study; however, in zone I, the definition was modified to permit a diagnosis of threshold at slightly less severity of ROP than required by the CRYO-ROP study because zone I threshold ROP, as defined in CRYO-ROP, progressed to poor retinal outcomes in 78% of eyes even with cryotherapy.[3]

A favorable ophthalmic endpoint was defined as regressing ROP in zone III for at least 2 successive weekly examinations, or full retinal vascularization. Ophthalmic outcomes at 3 months' corrected age were classified as: 1) unfavorable when there were findings of total or partial retinal detachment or when the visual axis was otherwise obstructed, 2) indeterminate when there was macular ectopia, or 3) favorable when there were only minor peripheral findings, laser or cryotherapy scars, or active ROP in zone II or III. The uncommon finding of continued active ROP at 3 months' corrected age was followed whenever possible with a repeat examination at 6 months' corrected age, although this situation had not been anticipated when the STOP-ROP protocol was developed. Whenever missed examinations or death caused incomplete endpoint dating or diagnosis of an eye's endpoint, all available eye data were provided to an ophthalmic endpoints committee of 3 ophthalmologists masked to the treatment assignment. The committee reached consensus on the outcome of each eye according to the following categories: 1) almost certainly reached adverse ophthalmic endpoint, 2) may have reached adverse ophthalmic endpoint, 3) indeterminate, 4) may have reached favorable ophthalmic endpoint, or 5) almost certainly reached favorable ophthalmic endpoint. Only consensus votes of 1 or 5 were used in any subsequent secondary analyses, and the committee was unaware of this analysis decision when they met (votes 2, 3, or 4 were treated as unknown).

Pediatric data were recorded at the time of randomization, at weekly intervals throughout the intervention period, and again at 3 months' corrected age. These data included duration of oxygen use and hospitalization after randomization; weight, length, and head circumference; use of diuretics, methylxanthines, or steroids; a checklist of specified adverse events; and episodes of rehospitalization. The age for achieving full nipple feeds was determined as the first day of 3 consecutive days of taking all enteral feedings by mouth. The questions for the Hollingshead classification of socioeconomic status (SES) were asked at discharge.[25] Adverse events, rehospitalizations, and deaths before 3 months' corrected age were reported as they occurred. The Revised Parental Denver Questionnaire was administered at 3 months' corrected age.[26]

All deaths and rehospitalizations were reviewed by 3 neonatologists masked to treatment assignment to determine whether pulmonary disease was the primary cause of death or rehospital-

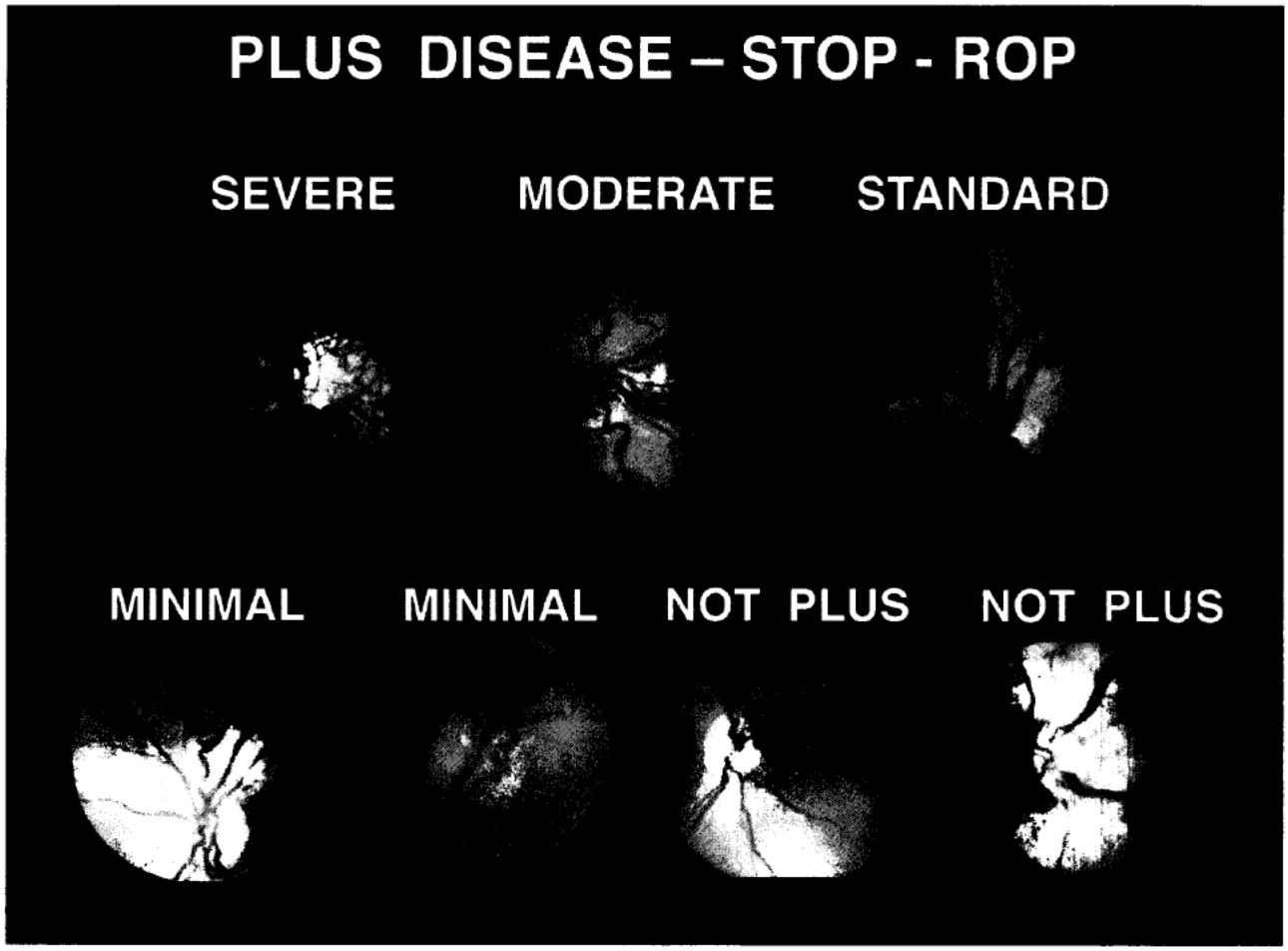

Fig 2. Standard photographs for the STOP-ROP study: fundus photographs of the posterior pole (visible with a direct ophthalmoscope), showing examples of mild to moderate posterior pole dilation/tortuosity and samples of retinas without this finding.

ization. Pneumonia/chronic lung disease (CLD) events were defined as probable or definite pneumonia, an acute exacerbation of CLD, or some combination of these 2 such that the study neonatologist could not distinguish between them.

Pulmonary Score

A composite pulmonary score was developed to describe the pulmonary status of each infant at baseline. The pulmonary score was calculated as:

$$\text{Pulmonary score} = (F_{IO_2})\ (\text{support}) + (\text{medications})$$

where F_{IO_2} is expressed as a fraction (room air = .21); support = 2.5 if on ventilator, 1.5 if on nasal or endotracheal continuous positive airway pressure (CPAP), and 1.0 if on nasal cannula, hood oxygen or off oxygen; and medications = .05 each for methylxanthines or intermittent diuretics, .10 for daily diuretics, .10 for inhaled steroids, and .20 for systemic steroids for CLD. Therefore, the pulmonary score could have a range of values between .21 (no pulmonary support, oxygen, or medications) and 2.85 (assuming that an infant would not be on both inhaled and systemic steroids). The baseline pulmonary score correlated well with pulmonary rehospitalizations, pulmonary deaths, and markers of CLD severity, such as duration of oxygen therapy (data not shown).

Sample Size and Data Monitoring

The progression rate to threshold was monitored by the Data and Safety Monitoring Committee at annual meetings. An early stopping guideline was constructed for ophthalmic benefit at an overall α-value of .025, and a stopping guideline for ophthalmic harm at an overall α-value of .10, allowing for repeated interim analyses[27] using the software of Reboussin (Madison, WI, University of Wisconsin, Department of Statistics). A sample size of 880 infants (to achieve 816 cases with final outcome data) was calculated as necessary to provide 90% power with an overall type I error rate of .025 to detect a one third reduction in progression to threshold disease or a 10% absolute reduction based on a predicted rate of progression of 30% in the conventional arm.[1] Adverse events were reviewed biweekly, and deaths were reviewed immediately by a neonatologist on the Data and Safety Monitoring Committee. All adverse events were reviewed at each meeting of the full Committee.

In 1997, the Data and Safety Monitoring Committee, after the enrollment of 449 children over 3.3 years, expressed concern about the ability of the study group to enroll the target number of 880 infants within 5 years, given consistent enrollment rates averaging 11.2 infants per month. Furthermore, new reports of nonrandomized case series in human infants suggesting a strong beneficial effect of supplemental oxygen,[28,29] as well as publication of additional animal model data,[30–35] supported the hypothesis of the STOP-ROP study, which might adversely affect enrollment. Calculations at that time showed that an enrollment of 633 infants completing the study would provide 83% power to detect a fall in the progression rate from 30% to 20%. The Committee members, who were not masked to study ophthalmic outcomes (although masked to treatment assignment) at the time of the review, recommended that recruitment continue through March 1999 with a revised enrollment goal of at least 633 infants. The final number of 649 enrollees, with ophthalmic endpoints available for 597, resulted in a power of ~80% against the designed alternative.

Statistical Analyses

Primary analyses were performed on all enrollees according to the assigned treatment arm (intention-to-treat) using the group-sequential method of Kim and DeMets.[27] Secondary categorical characteristics of the patients in the 2 arms were compared by χ^2 test, and group differences of continuous factors were compared with Student's t test and Wilcoxon rank-sum test. Logistic regression was used for the adjustment of progression rates for covariates. All P values presented are 2-sided and are unadjusted for the 5 interim examinations of the data, ie, are nominal P values, unless otherwise specified. Analyses were conducted with SAS software (SAS Institute, Cary, NC).[36]

RESULTS

Patients

Comparability of Enrolled and Registry Infants

From February 9, 1994, through March 31, 1999, 1847 infants with prethreshold ROP in at least 1 eye were registered at the participating centers. Of these, 634 (34%) were ineligible because either their pulse oximetry was greater than 94% in room air, or they had fatal or congenital eye anomalies (Fig 3). Of 1213 clinically eligible infants, 649 (54%) were enrolled. Reasons for nonenrollment were refusals of the family/guardians or the neonatologist (368), nonconfirmed prethreshold ROP (41), enrollment in conflicting studies (9), judgment that the infant was too ill to attempt randomization to the supplemental arm (28), inability of the family to comply with follow-up visits (41), imminent transfer to another hospital (8), and others. Of the ineligible infants, 99% had pulse oximetry greater than 94% in room air. Nonenrolled infants, including both those ineligible and those eligible but not enrolled (1198), weighed more at birth than enrolled infants (787 ± 287 vs 726 ± 160 g; $P < .001$) and had a slightly higher gestation at birth (25.7 ± 1.8 vs 25.4 ± 1.5 weeks; $P < .01$).

Comparability of Treatment Arms

Of the enrolled infants, 325 were randomized to the conventional arm, 324 to the supplemental arm, and their study completion rates are shown in Fig 3. The primary ophthalmic endpoint was available for 597 (92%) and was not recorded for 52 infants because of death (2), parental withdrawals from the study treatment (18), treatment with cryotherapy/laser before reaching ophthalmic endpoints (5), and missed eye examinations (27). Ophthalmic evaluations at 3 months' corrected age were completed for 600 infants and were unavailable for 49 because of death (16), withdrawal (31), and loss to follow-up (2). (Three additional infants in the supplemental arm not shown in the figure returned for just the neonatal portion of the 3-month evaluation). Rates of noncompletion were similar for both treatment arms (Fig 3).

Baseline demographic and pediatric characteristics are shown in Table 2, and ophthalmic baseline characteristics in Table 3. Randomization resulted in similar groups. Enrollment and randomization occurred at a PMA (PMA = gestational age at birth plus chronological age) of 35.4 ± 2.5 weeks (range: 30–48 weeks). The baseline pulmonary severity score and the mode of oxygen support were similar between the 2 arms. Many infants were on diuretics (54%) and methylxanthines (70%), and 29% had received steroids for CLD in the week before enrollment.

The ophthalmic baseline characteristics shown in Table 3 were also similar between the conventional and supplemental arms. There were no significant differences between the treatment arms in the number of infants enrolled in each ROP severity stratum or substratum. For the more severe forms of ROP represented in stratum A, 4.3% of enrollees had 1 eye at or beyond threshold (therefore, only 1 study eye), and 23.4% had 1 or both eyes with at least 1 clock hour of ROP in zone I. In stratum B, infants with

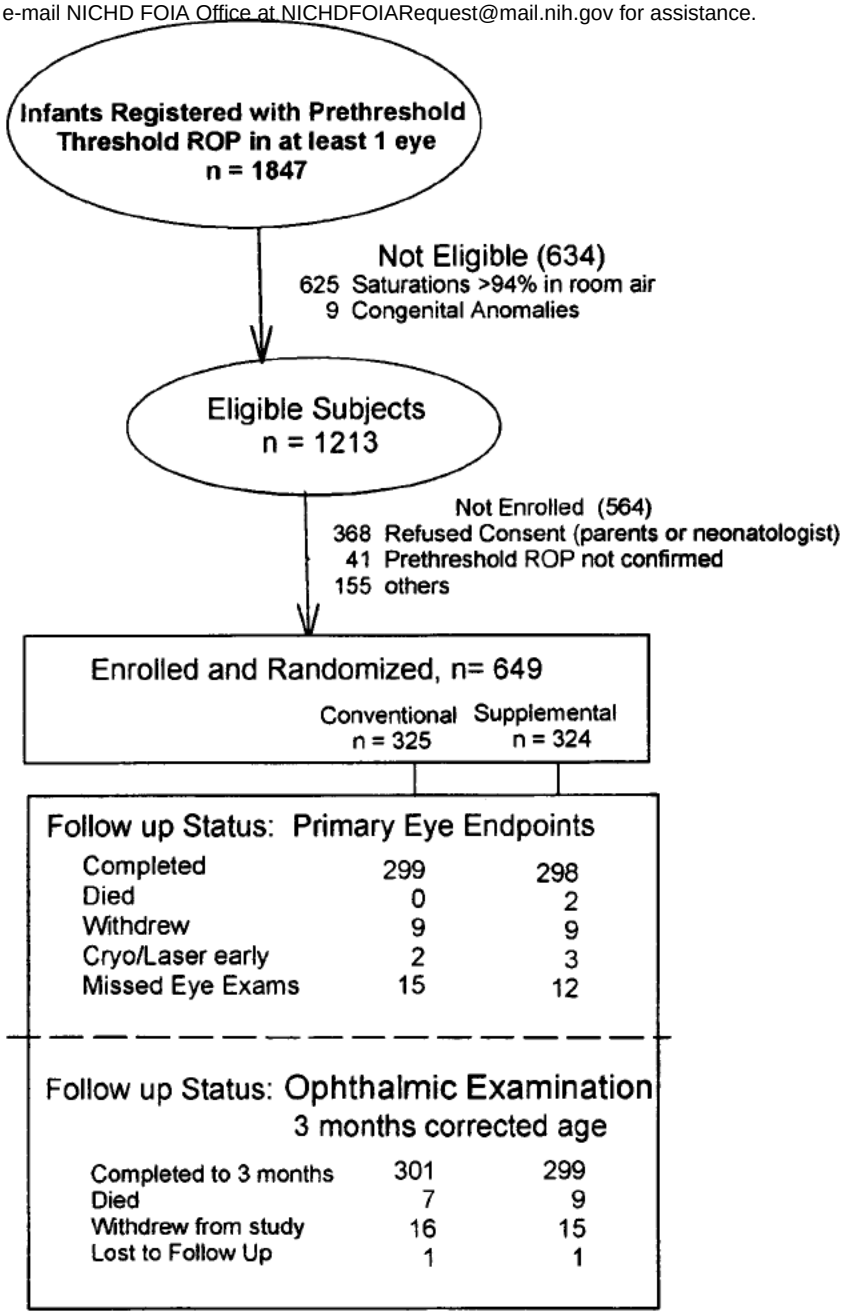

Fig 3. Patient enrollment flow diagram. There were several subjects without primary ophthalmic endpoints who nonetheless continued with follow-up examinations; therefore, there are more completed 3-month examinations than primary ophthalmic endpoints. Three additional supplemental infants completed the 3-month neonatal outcome examination, although they failed to complete the ophthalmic 3-month examination (not shown in figure).

zone II ROP in both eyes comprised 51% of all enrollees, and the remaining 21% entered the trial with the prethreshold eye's fellow eye at less than prethreshold ROP. There were no significant differences between the 2 arms in the number randomized within the first 24 hours after observing prethreshold ROP and in the numbers randomized after a longer period (Table 3). The elapsed time from the first diagnosis of prethreshold ROP to randomization was <24 hours in 33% of infants and >48 hours in 27% of infants.

Adherence to the Protocol

Oxygen requirements increased significantly for the infants randomized to the supplemental range. The average oxygen concentration increased from 36% ± 14% pretreatment to 46% ± 20%, 24 hours after randomization for those infants on a ventilator, CPAP, or hood oxygen; the average increase was 9.5% ± 16.5%. For infants on nasal cannula, the interactions between flow, infant size, and the oxygen concentration administered by cannula made estimation of the change in oxygen concentration more complex. Using the conversion formula of Benaron and Benitz,[37] average transformed oxygen concentration for infants on nasal cannula rose from 26% ± 6% before, to 31% ± 11% 24 hours after randomization to the supplemental arm; the average increase was 5% ± 9%. During the same 24-hour period, infants assigned to the conventional arm experienced a change from 36% ± 17% to 32% ± 15% in the infants on a ventilator, CPAP, or hood oxygen, and from 28% ± 10% to 26% ± 11% in the nasal cannula infants. (The 53 conventional and 25 supplemental

TABLE 2. Baseline Characteristics of Enrollees

	Number Enrolled		
	Conventional 325	Supplemental 324	Totals 649
Birth weight (g)*	721 ± 160	731 ± 161	726 ± 160
Gestational age (wk)*	25.4 ± 1.5	25.4 ± 1.5	25.4 ± 1.5
PMA (wk)*	35.3 ± 2.6	35.4 ± 2.5	35.4 ± 2.5
Weight at entry (g)*	1538 ± 445	1556 ± 442	1547 ± 443
Gender (% male)	53.9%	60.5%	57.2%
Race			
White	180 (55%)	179 (55%)	359 (55%)
Black	91 (28%)	101 (31%)	192 (30%)
Hispanic	31 (10%)	26 (8%)	57 (9%)
Others	23 (7%)	18 (6%)	41 (6%)
Pulmonary status			
Pulmonary score*	.53 ± .36	.56 ± .37	.55 ± .37
Ventilator	46 (14%)	57 (18%)	103 (16%)
CPAP or hood	57 (18%)	55 (17%)	112 (17%)
Nasal cannula	210 (64%)	203 (63%)	413 (64%)
No oxygen	12 (4%)	9 (3%)	21 (3%)
Medications			
Methylxanthines	68.6%	72.5%	70.1%
Diuretics	52.3%	57.1%	54.1%
CLD steroids†	28.1%	30.6%	29.3%
SES‡			
High (35–66)	27%	27%	27%
Intermediate (20–34)	30%	29%	29%
Low (0–19)	29%	26%	27%
Missing	14%	19%	16%

* Mean ± standard deviation.
† Steroids given systemically for CLD within the past week, not including inhaled steroids. Excludes 33 conventional and 40 supplemental infants from the early months of the study when data on the use of steroids were not being collected.
‡ SES by Hollingshead criteria,[25] as assessed at discharge.

TABLE 3. Baseline Ophthalmic Characteristics By Treatment Group

Characteristic	Conventional		Supplemental		Total	
	n	%	*n*	%	*n*	%
	325	100%	324	100%	649	100%
Stratum A—at least 1 eye PT ROP*						
Fellow eye worse than PT	14	4.3%	14	4.3%	28	4.3%
At least 1 eye zone I†	77	23.7%	75	23.2%	152	23.4%
Stratum B—at least 1 eye PT						
Both eyes zone II PT	167	51.4%	164	50.6%	331	51.0%
1 eye less than PT	67	20.6%	71	21.9%	138	21.3%
Infants with zone I ROP	88	27.1%	91	28.1%	179	27.6%
Infants with zone II ROP	237	72.9%	233	71.9%	470	72.4%
Plus disease infants‡	107	32.9%	112	34.6%	219	33.7%
Non-plus disease infants	218	67.1%	212	65.4%	430	66.3%
Time from first§ PT diagnosis to randomization (infants in category)						
≤24 h	115	35.5%	100	31.6%	215	33.2%
>24, ≤48 h	127	39.2%	128	39.6%	255	39.4%
>48 h	82	25.3%	95	29.4%	177	27.4%
Missing	1		1		2	

* PT indicates prethreshold retinopathy of prematurity.
† Note that in stratum A, infants with bilateral zone I ROP and 1 eye already at threshold or beyond, are categorized as "fellow eye worse than prethreshold."
‡ Plus disease is defined as present when there is posterior pole vascular dilation and tortuosity in at least 2 quadrants. An infant is a plus disease infant if at least 1 study eye has plus disease at baseline. Similarly, an infant is a zone I infant if at least 1 study eye has zone I ROP.
§ "First PT diagnosis" is the date/time of the first examination that showed prethreshold ROP in at least 1 eye that was subsequently confirmed on a second examination.

infants who changed mode of support in 1 direction or the other between nasal cannula and ventilator/CPAP/hood during the first 24 hours after randomization are not included in these calculations.)

Table 4 demonstrates that the distributions of median saturations achieved over the first 2 weeks after randomization were different for the 2 treatment arms. During the first 2 weeks, only 8.0% of median saturations for infants assigned to the conventional arm were in the supplemental range or higher, and

TABLE 4. Distribution of Infants According to Median Pulse Oximetry Over the First Two Weeks on Study

Median Pulse Oximetry Value Over First 2 Weeks, (%)	Conventional Arm* $n = 325$	Supplemental Arm* $n = 324$
<89	.0	.0
89	.0	.0
90	.3	.0
91	16.9	.0
92	34.5	.3
93	19.1	.3
94	14.5	1.2
95	6.2	6.8
96	3.7	23.5
97	2.8	56.5
98	.9	9.6
99	.0	.6
100	.6	.3
Missing	.6	.9

The | symbols indicate the targeted range of saturation values for each arm of the study.
* Each study arm column gives the percentage of all subjects in that column whose median pulse oximetry over the first 2 weeks on study was at the level shown in the left hand column.

only 1.8% of median saturations of infants assigned to supplemental therapy were in the conventional range or lower. Pulse oximetry was recorded from all enrollees for these first 2 weeks of study participation, but beyond this period, as the eyes reached study endpoints, fewer infants remained on equipment to contribute to the accumulating oximetry data. In addition, as some infants in the conventional arm had resolution of their CLD, their saturations became greater than 95% while breathing room air. Figure 4 shows the smoothed overall frequency distribution of the saturation values (1 reading every 40 seconds) for the full period until ophthalmic endpoints for all infants enrolled. These data also include the 81 conventional and 85 supplemental infants who continued to use study equipment at home. Refusal of the parents or guardians to take the study equipment home on the day of discharge was a primary cause of premature cessation of pulse oximetry and study assigned oxygenation, occurring in 26 conventional and 24 supplemental subjects. Many of these families/guardians were willing to continue returning for weekly follow-up examinations, and therefore, were not withdrawn from the study. Comparison of the SES of families who refused equipment, with those that accepted it at home, showed no relationship between SES and refusal of this major home challenge, nor success in remaining in the target zones at home (data not shown).

Ophthalmic Outcome Data

The primary outcome, the proportion of infants with at least 1 eye progressing to confirmed threshold ROP, is shown by treatment arm in Table 5 for all infants and for subgroups of infants defined by baseline ophthalmic characteristics. Overall, 48.5% (145/299) of infants with study endpoints and assigned to the conventional arm progressed to confirmed threshold ROP in at least 1 eye, compared with 40.9%

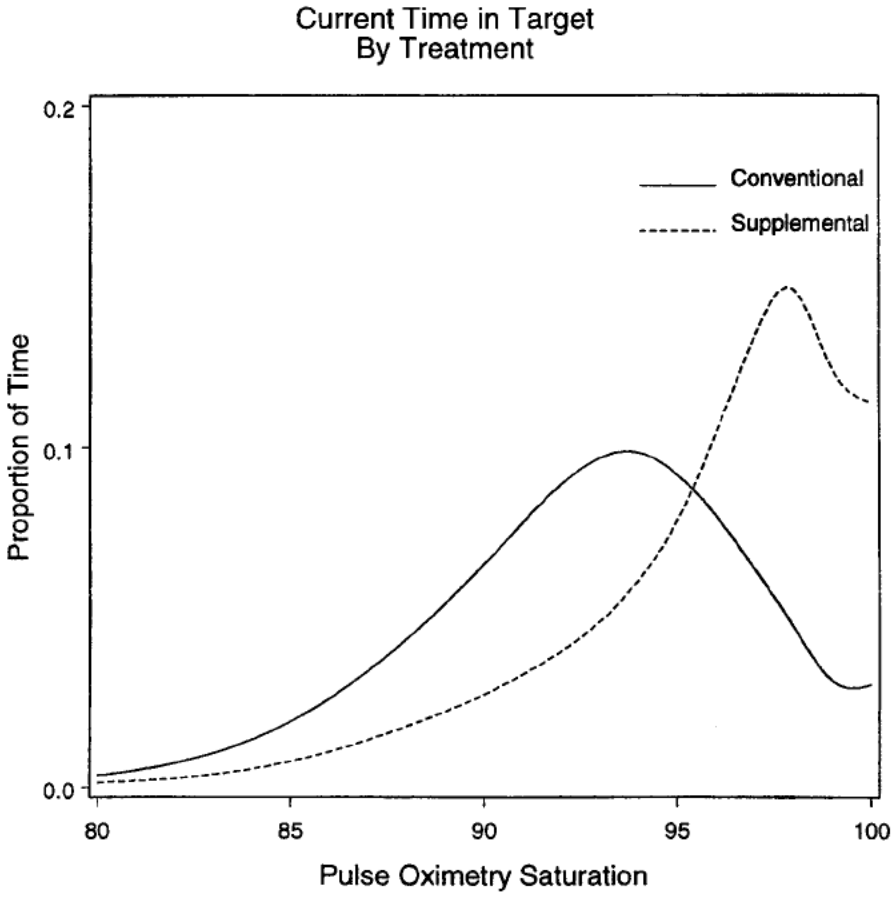

Fig 4. Smoothed frequency distribution of pulse oximetry saturation values for the conventional and supplemental oxygen arms throughout the duration of time on study equipment. Pulse oximetry saturation values were recorded to disk for later analysis once every 40 seconds throughout the time an infant remained on study equipment (range: 2–25 weeks).

TABLE 5. Progression to Threshold ROP* by Ophthalmic Characteristics and Treatment Assignment

Characteristic	Conventional		Supplemental		Total	
	n	%	*n*	%	*n*	%
Enrolled	325	100%	324	100%	649	100%
Without eye endpoints†	26	8%	26	8%	52	8%
With eye endpoints†	299	92%	298	92%	597	92%
Infants with eye endpoints†	299	100%	298	100%	597	100%
Progression to threshold	145	48%	122	41%	267	45%
Stratum A (progressed/total)	46/84	55%	37/81	46%	83/165	50%
Fellow eye worse than PT‡	8/13	62%	8/14	57%	16/27	59%
At least 1 study eye zone I	38/71	54%	29/67	43%	67/138	49%
Stratum B (progressed/total)	99/215	46%	85/217	39%	184/432	43%
Both eyes zone II PT	80/152	53%	66/152	43%	146/304	48%
1 eye less than PT	19/63	30%	19/65	29%	38/128	30%
Infants with zone I ROP, in at least 1 eye	46/82	56%	41/83	49%	87/165	53%
Infants with zone II ROP	99/217	46%	81/215	37%	180/432	42%
Plus disease infants§	54/103	52%	59/103	57%	113/206	55%
Non-plus disease infants§	91/196	46%	63/195	32%	154/391	39%
Time elapsed from randomization‖						
All study eyes						
To adverse outcome, wk	2.4 ± 2.0		2.7 ± 2.0		2.5 ± 2.0	
To favorable if resolved, wk	9.0 ± 3.8		9.5 ± 4.0		9.2 ± 3.9	
Eyes <PT ROP at randomization	14/62 (22.6%)		14/61 (23.0%)		28/123 (22.8%)	
To adverse outcome, wk	1.7 ± 1.1		3.2 ± 1.3		2.4 ± 1.4	
To favorable outcome, wk	7.8 ± 3.8		8.2 ± 3.9		8.0 ± 3.8	
Eyes without plus disease						
To adverse outcome, wk	2.3 ± 2.1		2.7 ± 2.0		2.5 ± 2.1	
To favorable outcome, wk	8.9 ± 4.0		9.5 ± 4.1		9.2 ± 4.1	
Eyes with plus disease						
To adverse outcome, wk	1.6 ± 1.0		2.2 ± 1.9		1.9 ± 1.6	
To favorable outcome, wk	7.5 ± 2.9		7.1 ± 3.3		7.3 ± 3.1	

* Infant ophthalmic outcomes based on progression of at least 1 study eye to threshold ROP. If an infant entered the study with 1 eye already at threshold or worse, that eye was not a study eye, and the infant's outcome is based on only the study eye.
† "Eye endpoints" means that for that infant, the primary endpoint of either 1) at least 1 eye progressing to threshold, or 2) all study eyes not progressing to threshold is known.
‡ PT indicates prethreshold ROP.
§ "Plus disease infants" are those who have at least 2 quadrants of posterior pole dilation/tortuosity in at least 1 study eye, whereas "non-plus disease infants" have all study eyes with 0 or 1 quadrant of posterior pole dilation/tortuosity.
‖ Mean ± standard deviation.

(122/298) in the supplemental arm. The difference between treatment arms was not significant at the designed 1-tailed α-level of .025, as adjusted for sequential testing. However, the difference was still suggestive, with a 1-tailed P value adjusted for repeated interim analyses of .032.[38] When eyes whose outcomes could be assigned by the Ophthalmic Endpoints Committee were included (31 infants: 15 conventional and 16 supplemental), the progression rates remained similar: 46.2% (145/314) and 39.5% (124/314) for the conventional and supplemental arms, respectively (data not shown).

Analysis by stratum or zone of baseline ROP yielded similar results. The high severity ROP stratum A infants progressed to threshold more frequently than the lower risk stratum B infants (50% vs 43% overall). Higher rates of progression in the conventional arm than in the supplemental arm were observed for both ROP severity strata (55%–46% in stratum A and from 46%–39% in stratum B). When severity was alternatively examined by zone of prethreshold ROP, progression rates also were lower in the supplemental arm (56% vs 49% for zone I and 46% vs 37% for zone II; conventional vs supplemental, respectively); however, none of these differences were statistically significant. In contrast, when progression rates were examined in relation to plus disease, the subgroup analysis revealed a difference. Infants without plus disease in either study eye progressed to threshold 46% versus 32% of the time in the conventional and supplemental arms, respectively (P = .004). When at least 2 quadrants of posterior pole dilation/tortuosity were present in either study eye at baseline, 52% of conventional versus 57% of supplemental infants had at least 1 eye progress to threshold (P = .484).

Adverse outcomes occurred soon after randomization in both groups as shown in Fig 5A, and the elapsed time from study entry to adverse ophthalmic endpoints was slightly longer in the supplemental arm compared with the conventional arm. Mean progression time to threshold disease was 2.4 weeks for eyes in the conventional arm and 2.7 weeks for eyes in the supplemental arm. Eyes with plus disease at study entry progressed to threshold disease most rapidly, at a mean of 1.6 and 2.2 weeks in the conventional arm and supplemental arm, respectively. Eyes without plus disease took somewhat longer (mean of 2.3 weeks and 2.7 weeks, respectively; Table 5). Achieving a favorable outcome took longer (Fig 5B), and the time to full vascularization or zone III vessels on 2 consecutive examinations in eyes

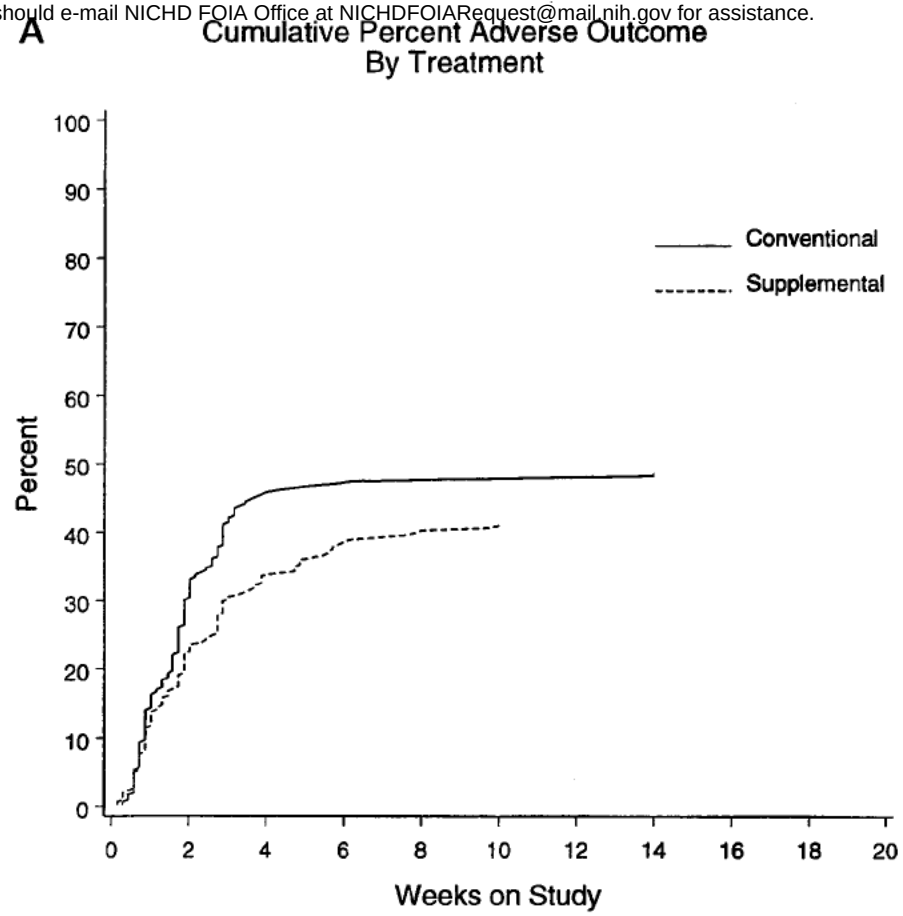

Fig 5. Cumulative rate curves demonstrating the differences in both the proportion and timing of adverse (A) and favorable (B) ophthalmic outcomes by study arm.

without progression to threshold disease occurred in the conventional arm at a mean of 9.0 weeks and in the supplemental arm at a mean of 9.5 weeks. Threshold ROP, when it occurred, was diagnosed at an average PMA of 36.8 weeks (range: 31.6–50.9 weeks) in the conventional arm, and an average of 37.3 weeks' PMA (range: 32.3–45.1 weeks) in the supplemental arm (data not shown in table).

Multiple regression analysis was conducted to adjust for minor variations in baseline characteristics with both simple and complex models. The complex model included treatment assignment, ROP stratum, race, gender, gestational age, small for gestational age status, the baseline pulmonary severity score, plus disease, late versus on-time enrollment, degree of compliance with assigned saturations, interactions of these variables with treatment assignment, and study center. The analysis did not alter the conclusions, but did confirm that both black race (odds ratio [OR]: .44; 95% confidence interval [CI]: .20,.94) and higher gestational age (OR: .80 per week; 95% CI: .66,.98) provide important significant protective effects in reducing the chance of progression of prethreshold ROP to threshold ROP, regardless of treatment arm, while having 2 or more quadrants of posterior pole dilation/tortuosity (plus disease) increased the risk of progression to threshold (OR: 1.71; 95% CI: .95,3.10). In the simplified model, the OR for the supplemental arm after adjustment for ROP risk stratum, plus disease, race, and gestational age was .72 (95% CI: .52,1.01).

Peripheral ablation utilized laser therapy in 93% of treated eyes (73% diode and 20% Argon) and cryotherapy alone in 7%. Four percent of treated eyes received both laser and cryotherapy. Final ophthalmic outcomes based on all study eyes at 3 months' corrected age (or 6 months for 12 conventional and 18 supplemental eyes) revealed adverse outcomes (partial or total retinal detachment, retinal folds, or obstruction of the visual axis) in 4.4% of the study eyes in the conventional and 4.1% in the supplemental arms, and macular ectopia in an additional 3.9% of the study eyes of the conventional arm and 3.9% of the study eyes of the supplemental arm. Among just those eyes that developed threshold ROP and were treated with peripheral surgical ablation, 9.2% in the conventional arm and 13.2% in the supplemental arm had adverse ophthalmic outcomes at 3 to 6 months (excludes macular ectopia that occurred in 6.3% of conventional and 7.7% of supplemental laser/cyro-treated eyes).

Pediatric Outcomes

We hypothesized that infants in the supplemental arm would grow and gain weight faster than infants in the conventional arm, but there were no differences between their growth rates during the initial first 2 weeks, later during the hospitalization period (data not shown), or at 3 months' corrected age (Table 6).

However, markers of CLD severity both during hospitalization and remaining at 3 months' corrected age (50 weeks' PMA) suggest a somewhat worse pulmonary status in the supplemental arm after randomization, although there were no differences in the baseline status measures (Table 2). As shown in Table 6, the conventional arm had fewer infants with 1 or more episodes of pneumonia or CLD exacerbation than did the supplemental arm, 25 (8.5%) versus 38 (13.2%; $P = .066$), and there were also fewer total episodes in the conventional arm (29 vs 51). Using the baseline pulmonary scores to further examine this, infants were divided into higher and lower pulmonary risks at the overall median pulmonary score of .430. The difference in pneumonia/CLD events was confined to the infants with the higher half of the pulmonary scores (10.6% in the conventional arm vs 18.7% in the supplemental arm; $P = .051$) and did not differ among the infants with the lower half of the pulmonary scores (6.5% in the conventional arm vs 6.8% in the supplemental arm; $P = .93$; data not in table). Rehospitalization rates for pulmonary causes (excluding for apnea alone), and death rates from pulmonary causes were similar in the 2 arms (Table 6). However, at the 3-month examination (50 weeks' PMA), more infants in the supplemental arm remained hospitalized (12.7% vs 6.8%; $P = .012$), on oxygen (46.8% vs 37.0%; $P = .020$), and on diuretics (35.8% vs 24.4%; $P = .002$). The proportion of infants who experienced any 1 or more of these adverse pulmonary events by 3 months' corrected age as defined by remaining hospitalized, remaining on study equipment, oxygen, steroids, methylxanthines, or diuretics was significantly higher in the supplemental arm than in the conventional arm (57% vs 46%, respectively; $P = .005$). Regression analysis adjusting for the important baseline covariates of race, ROP severity, gestational age, and pulmonary status did not change the significance of these findings.

Adverse events from sepsis without pneumonia did not differ between the 2 arms, and survival through the 3-month examination was similar (97.8% conventional vs 97.2% supplemental). Mean PMA at discharge for those infants going home was the same in both arms at 41 ± 3 weeks (range: 35–56), and infants in both arms were able to take oral feeds without a gastric tube at the mean PMA of 39 weeks. At the 3-month follow-up examination, developmental levels as assessed by the Revised Parental Denver Questionnaire were similar (equivalent ages = 3.5 ± 1.4 months in the conventional arm vs 3.4 ± 1.4 months in the supplemental arm).

DISCUSSION

These findings demonstrate that supplemental oxygen, as used in this study for prethreshold ROP, did not significantly decrease the proportion of infants who have at least 1 eye progress to threshold ROP, although the differences were close to nominal statistical significance. Using the observed conventional progression rate of 48%, the study has a power of 70% against a 10-percentage point absolute difference, and a power of 98% against a one third reduction, adjusting for the use of repeated interim analyses as described above. The resultant power is lower than expected because the adverse ophthalmic outcome rate in the conventional group was higher than expected.

TABLE 6. Pediatric Outcomes Between Randomization and Three Months' Corrected Age*

	Conventional $n = 325$	Supplemental $n = 324$
Event occurring after randomization		
Weight gain over the first 2 wk (g; mean ± standard deviation)	291 ± 137	278 ± 143
Length gain over the first 2 wk (cm; mean ± standard deviation)	1.8 ± 1.8	1.7 ± 2.0
Head circumference increase the 1st 2 wk (cm; mean ± standard deviation)	1.6 ± 1.0	1.4 ± .9
PMA at discharge home† (wk; mean ± standard deviation)	41.1 ± 3.3	41.3 ± 3.4
PMA to achieve oral feeding‡ (wk; mean ± standard deviation)	39.0 ± 3.5	38.9 ± 3.6
Infants with pneumonia/CLD events (total # of events)§	25 (29)	38 (51)
Infants with sepsis, but no pneumonia/CLD (total # events)	12 (12)	11 (11)
Infants with apnea/bradys triple baseline (total # events)	26 (36)	30 (33)
Outcomes at the 3-month corrected age window‖		
Remained hospitalized¶ (%)	6.8%	12.7%
Remained on study equipment (%)	3.1%	3.4%
Remained on oxygen (%)	37.3%	46.8%
Remained on steroids (%)	12.5%	14.2%
Remained on methylxanthines (%)	13.5%	14.7%
Remained on diuretics (%)	24.4%	35.8%
Infants with any 1 of the above, # of infants (%)#	148 (45.5%)	183 (56.5%)
Outcomes at 3 months' corrected age examination	$n = 301$	$n = 302$
Infants rehospitalized (# of all rehospitalizations)	99 (132)	87 (116)
Infants rehospitalized for pulmonary reasons, not apnea (# of all rehospitalizations)	46 (53)	41 (49)
All deaths, *n* (pulmonary cause of death, *n*)	7 (3)	9 (5)
Room air saturations too low to test, *n* (%)	17 (6%)	35 (12%)
Room air oxygen saturation for those tested, mean ± standard deviation	95.3 ± 4.7%	94.6 ± 7.7%
Weight gain from randomization (mean ± standard deviation; kg)	2.96 ± 1.00	2.88 ± 1.05
R-PDQ developmental level** (mean ± standard deviation; mo)	3.5 ± 1.4	3.4 ± 1.4

* Corrected age indicates months after the date an infant should have been born at full term (3 months' corrected = 52 weeks' PMA).
† Limited to infants who were discharged to home (ie, excludes deaths, loss to follow-up, and those remaining hospitalized at the 3-month examination).
‡ Excludes 16 conventional and 33 supplemental infants who were not yet feeding by mouth by 50 weeks' PMA, 2 conventional and 7 supplemental infants who died before oral feeds, and 6 conventional and 7 supplemental infants with incomplete data. Oral feeds means that the infant was taking all enteral feedings by nipple (bottle or breast).
§ Excludes 30 conventional and 36 supplemental infants recruited early in the trial for whom these data were not collected.
‖ The 3-month corrected age window was a target of 12 ± 2 weeks after due date, or 50 to 54 weeks' PMA. Outcomes are reported as of 50 weeks' PMA to permit comparisons as some infants were examined late in the window or outside this window.
¶ Values exclude 31 infants with missing data at 50 weeks' PMA attributable to loss to follow-up (14 conventional and 17 supplemental).
# Number of infants, and percent of all enrollees represented by any 1 or more of the 3-month events.
** R-PDQ indicates the Revised Parental Denver Questionnaire.[26]

In STOP-ROP, the observed rate of progression from prethreshold to threshold (48%) in the conventional arm is higher than reported in the CRYO-ROP study (33%) for a number of reasons that can be identified. The eligibility criteria for STOP-ROP excluded nearly half of the infants who would have been included in the CRYO-ROP study, and these were the ones that did not require oxygen and had less severe lung disease at the time of prethreshold ROP. The STOP-ROP enrollees had lower birth weights than the CRYO-ROP infants (726 g in STOP-ROP vs ~850 g for CRYO-ROP prethreshold).[1] During the CRYO-ROP study, borderline threshold cases were judged as not threshold, to avoid treating eyes with an unproven intervention. Because peripheral ablation has been demonstrated to be effective for threshold ROP, this is no longer true, and as in clinical practice, the STOP-ROP study judged in favor of the diagnosis of threshold disease in borderline cases. Finally, the differences in the STOP-ROP definition of threshold ROP in zone I (see Table 1) would result in more infants being diagnosed with threshold ROP during the STOP-ROP trial.

The STOP-ROP results differ from the 2 smaller case series in the literature in which supplemental oxygen for infants with prethreshold ROP was associated with a high regression rate of prethreshold ROP without the need for ablative retinal surgery.[28,29] Some of the possible explanations are differences in patient selection, level of oxygen administration, timing of the intervention, and use of historical controls in the case series. Infants in these case series may have had milder ROP than those enrolled in STOP-ROP, and the effect of that would be higher progression rates in STOP-ROP. The average birth weight of the infants in that series was 814 g, heavier than the 726-g average birth weight of infants enrolled in STOP-ROP, and therefore, at lower risk for severe ROP. In the Gaynon et al[28] series, if infants were mostly detected as having pretheshold ROP before developing plus disease, the findings in that series and the subgroup of infants in STOP-ROP without plus disease would be more consistent. Large differences in reported improvements between historically controlled case series and randomized trials are well recognized and are usually attributed to changes in several aspects of medical care over time, as well as patient selection. STOP-ROP expended considerable effort to maximize the time infants were in their targeted ranges of saturation and not at saturation levels of 100%. In contrast, however, the saturation targets were "a minimum of 99%" in the Gaynon et al study,[28] and "a minimum of 98%" in the Seiberth et

al report.[29] Thus, infants in those 2 series probably had higher average saturation levels than the STOP-ROP supplemental group. To compare the target range of the supplemental arm in STOP-ROP as measured by the Ohmeda 3740 oximeter with these other 2 studies, it could be argued that 1.6 saturation points should be added to the STOP-ROP range to make the saturation monitor readings equivalent. If this is done, the STOP-ROP supplemental range becomes 97.6% to 100% saturation, even closer to the reported series and, therefore, not an explanation of differences.

Another alternative explanation may be in the timing of treatment. If immediate application of the supplemental oxygen at prethreshold diagnosis would provide maximum benefit, it could be argued that use in standard practice would result in earlier and possibly more effective treatment of eyes with prethreshold ROP. Gaynon reports (D. L. Phelps, personal communication, October 1999) that ROP screening was performed at weekly intervals in their series, which could be expected to reduce the number of infants reaching plus disease before beginning oxygen treatment. Screening examinations before prethreshold identification were usually performed every 2 weeks in the STOP-ROP centers, consistent with the AAP recommendations. In addition, the process of obtaining both an independent confirming examination and informed consent of the family or guardians resulted in delays between the first time that prethreshold ROP was observed and the start of the study intervention. In approximately one quarter of the cases, this was >48 hours.

Oxygen requirements go up by ~5 to 9 percentage points when changing to supplemental oxygen from the conventional range, emphasizing that infants truly receive more oxygen when assigned to the supplemental arm. We had not expected that pulmonary events of pneumonia and/or CLD exacerbations were going to be 1.8 times more likely to occur in the supplemental arm. The absolute increase in acute pulmonary events of 7.3% gives a number-needed-to-treat calculation of 1 more pneumonia/CLD episode for each 13.7 infants treated with supplemental oxygen. The ROP progression data give a number-needed-to-treat of 13.2 infants to prevent 1 case of progression to threshold ROP. By this analysis, one could expect ~1 episode of pneumonia/CLD exacerbation for each case of peripheral ablative surgery that might be prevented. That might be regarded as a reasonable trade-off by most neonatologists and ophthalmologists, but the condition of the infants at 3 months' corrected age must also be considered. At that time, 97% of subjects were off the study assigned treatments, and those in the supplemental arm continued to need more oxygen and diuretics, and a greater number remained hospitalized. Our data suggest that the magnitude of any benefit from supplemental oxygen in reducing the need for surgery is likely to be on the order of 7% to 14%, with no reduction in the number of retinal detachments. The potential long-term advantage of avoiding peripheral ablative surgery for ROP is unknown, but to the extent long-term side effects might occur, even a small reduction in surgery rates may be of value. The potential long-term effects, both of costs and to the families, of prolonging hospitalization from worsened lung disease also should be considered.

Our original hypothesis was not only that supplemental oxygen would prove beneficial for the eyes of infants with prethreshold ROP whose pulse oximetry in room air is <94%, but in addition, that it would be beneficial for CLD, resulting in better growth and lower pulmonary vascular resistance.[39,40] However, Supplemental oxygen at a target range of 96% to 99% saturation seemed to have deleterious effects on CLD in some infants, with no change in growth or neuromotor development. Previous reports of an improvement in weight gain and resolution of cor pulmonale with oxygen supplementation could be explained if saturation levels in the control infants of those studies were even lower than the STOP-ROP conventional range. This is certainly possible, because those reports date from periods preceding the routine availability of continuous pulse oximetry. Fortunately, others are investigating this question in a carefully controlled randomized trial in Australia. The Benefits of Oxygen Saturation Targeting Trial is currently enrolling infants in a test of the safety and efficacy of supplemental oxygen for infants with CLD. ROP is not an entry criterion in that study, but will be examined as a secondary outcome (D. Henderson-Smart, personal communication, 1999).

These results provide valuable data for the clinician. The STOP-ROP data clearly demonstrate that oxygen, at saturation levels of 96% to 99% does not increase the severity of ROP in the eyes of infants with prethreshold ROP, even in the 123 eyes with ROP of less than pretheshold severity at randomization. There are no data, however, to suggest that the higher saturation levels are safe for the early immature eye that does not yet have established ROP. The reported data apply only to infants who are well beyond the initial weeks after birth and must not be interpreted as showing safety of supplemental levels of oxygen at younger ages.

The present study does not rule out a potential small reduction in the rate of ROP progression with supplemental oxygen, and a subgroup analysis suggests that supplemental oxygen, as used in this study, may be more effective in pretheshold ROP without plus disease. However, secondary analyses, not prespecified, must be cautiously interpreted and require additional study. The predictive value of various possible definitions of prethreshold ROP have not been systematically studied and reported but could prove very important and should be investigated. The data show a modest deleterious effect of supplemental oxygen on CLD in some infants with more severe lung disease at baseline. Therefore, clinicians must consider which patients might tolerate the added pulmonary risk of supplemental oxygen as a therapeutic intervention for their ROP. If an infant requires saturations of 96% to 99% for cardiopulmonary reasons, fear about causing worse ROP is not a reason to withhold the oxygen. Results from other studies, such as the Benefits of Oxygen Satura-

tion Targeting Trial, may help further our understanding of the effects of supplemental oxygen in infants with CLD.

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Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), A Randomized, Controlled Trial. I: Primary Outcomes

The STOP-ROP Multicenter Study Group

Pediatrics 2000;105;295-310
DOI: 10.1542/peds.105.2.295

From:	Neil Finer
To:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; Das, Abhik; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Maynard Rasmussen"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Cc:	"Hastings, Betty J."
Date:	Monday, December 05, 2005 6:24:43 PM
Attachments:	Daily FiO2 for first 14 days.doc Response to DSMC Steering Dec 5.doc Avery Letter Dec 05.doc

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Hello Everyone

We got some new FiO2 data that I had asked Marie to run – somewhat of a gamble – but I think it paid off – The 85-89% infants have an absolute 10% increase (36% vs 26%) in room air during the first 14 days compared to the 91-95% group. I have also decided that we should lower the high alarm 1% to 94% as this will force the 85-89% infants more into the range. For the 91-95% infants, once their oximeter is more than 92 reading they are at 95% and if we want to reduce their time > 95% this would work. Plus I think we want an iron-clad response to the DSMC and thus should do everything possible to convince them to allow this study to proceed.

Please review this and let me know if you are OK with the current letter and response.

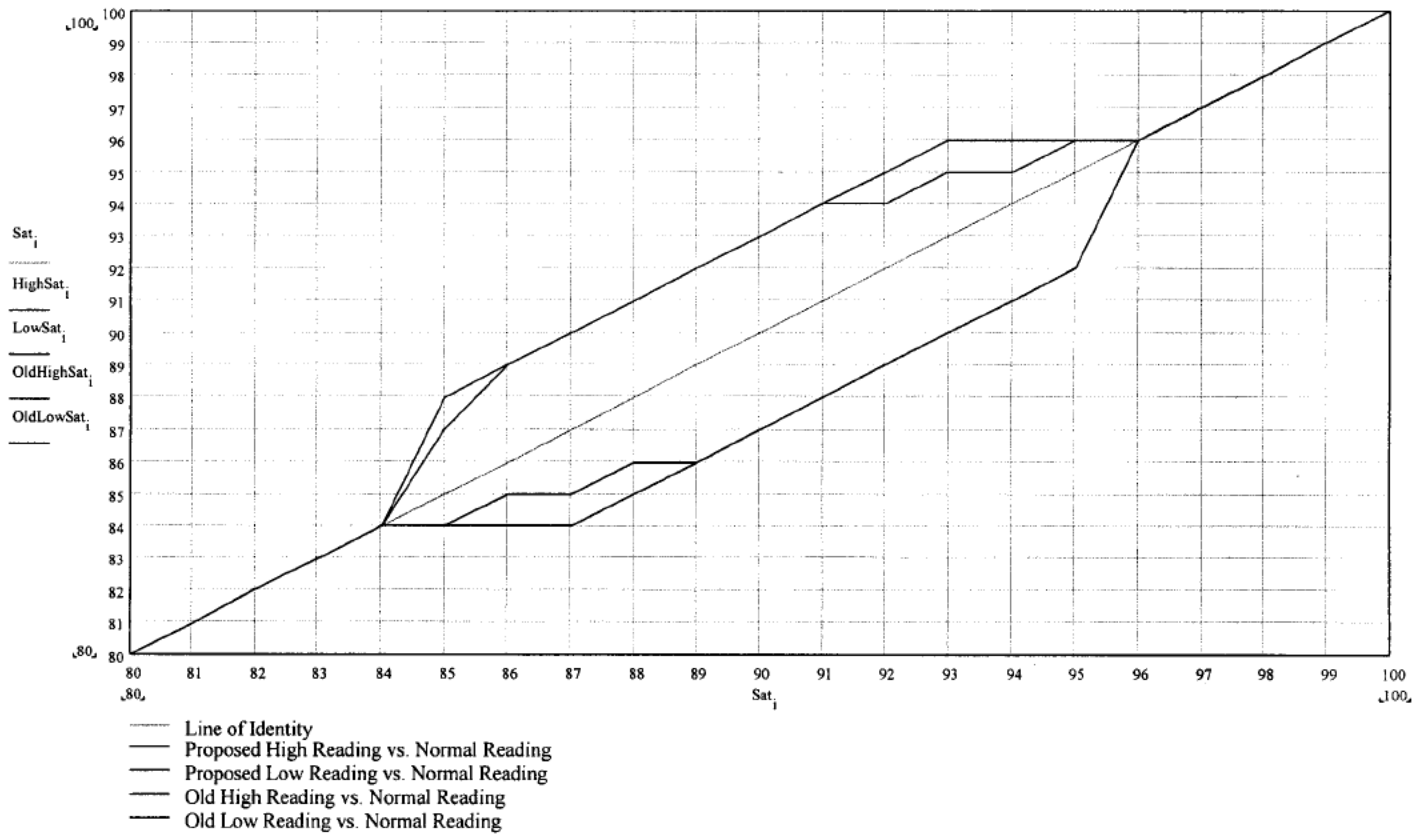
I would like to allow Betty to send all this to the DSMC tomorrow morning.

Thanks for taking the time to consider these issues.

Neil

Converting Actual Readings to Low and High Readings

Actual Reading	To Low Reading	To High Reading
	85% -89%	91%-95%
100	100	100
99	99	99
98	98	98
97	97	97
96	96	96
95	92	96
94	91	96
93	90	96
92	89	95
91	88	94
90	87	93
89	86	92
88	85	91
87	84	90
86	84	89
85	84	88
84	84	84
83	83	83
82	82	82
81	81	81
80	80	80
etc	etc	etc



The Low, Actual & High Reading oximeters synchronize for values greater than or equal to 96 % and less than or equal to 84 %.

In the Actual range of 87 % to 95 %, the Low Reading Oximeter displays a value 3 points below actual.

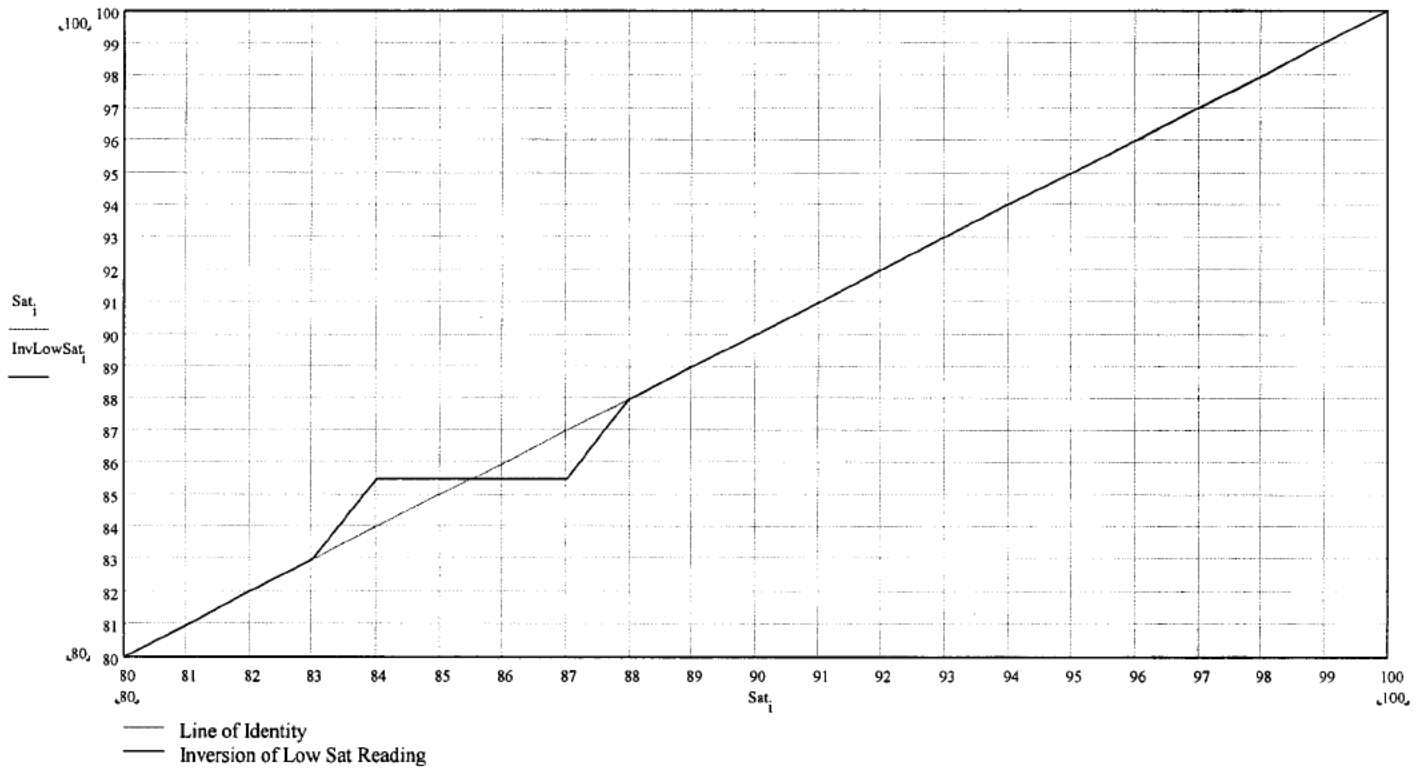
In the Actual range of 85 % to 93 %, the High Reading Oximeter displays a value 3 points above actual.

Converting Low Readings to Normal Readings

91% - 95%

Low Reading	To Normal Reading
100	100
99	99
98	98
97	97
96	96
95	95.75
94	95.50
93	95.25
92	95
91	94
90	93
89	92
88	91
87	90
86	89
85	88
84	85.5
83	83
82	82
81	81
80	80
etc	etc

Applying the above inversion yields the following performance:



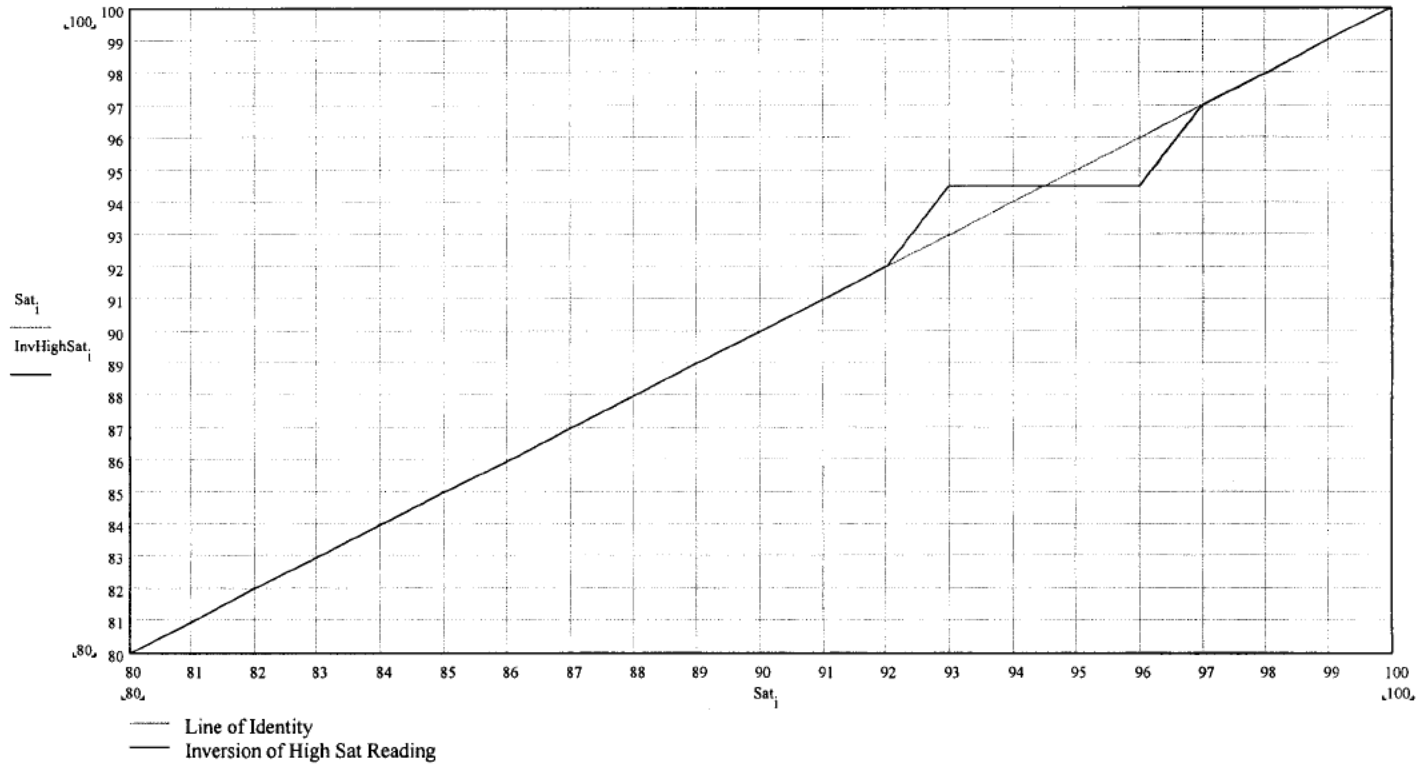
The inversion has no error above and below an actual reading of 88 % and 83 %, respectively. In between these limits, the inversion error does not exceed 1.5 %. Subjects are typically kept in the region of 91 % (88 % + 3 %) to 95 % (92 % + 3 %).

Converting High Readings to Actual Readings

85% - 89%

High Reading	To Actual Reading
100	100
99	99
98	98
97	97
96	94.5
95	92
94	91
93	90
92	89
91	88
90	87
89	86
88	85
87	84.75
86	84.50
85	84.25
84	84
83	83
82	82
81	81
80	80
etc	etc

Applying the above inversion yields the following performance:



The inversion has no error above and below an actual reading of 97 % and 92 %, respectively. In between these limits, the inversion error does not exceed 1.5 %. Subjects are typically kept in the region of 85 % (88 % - 3 %) to 89 % (92 % - 3 %).

Daily FiO2 values for first 14 days of life
Average daily FiO2 for each infant (average of 3 FiO2 measurements on SUPP05)
Includes data on 155 infants (73 High target, 82 Low target) for whom pulse oximeter data is available
12-5-05

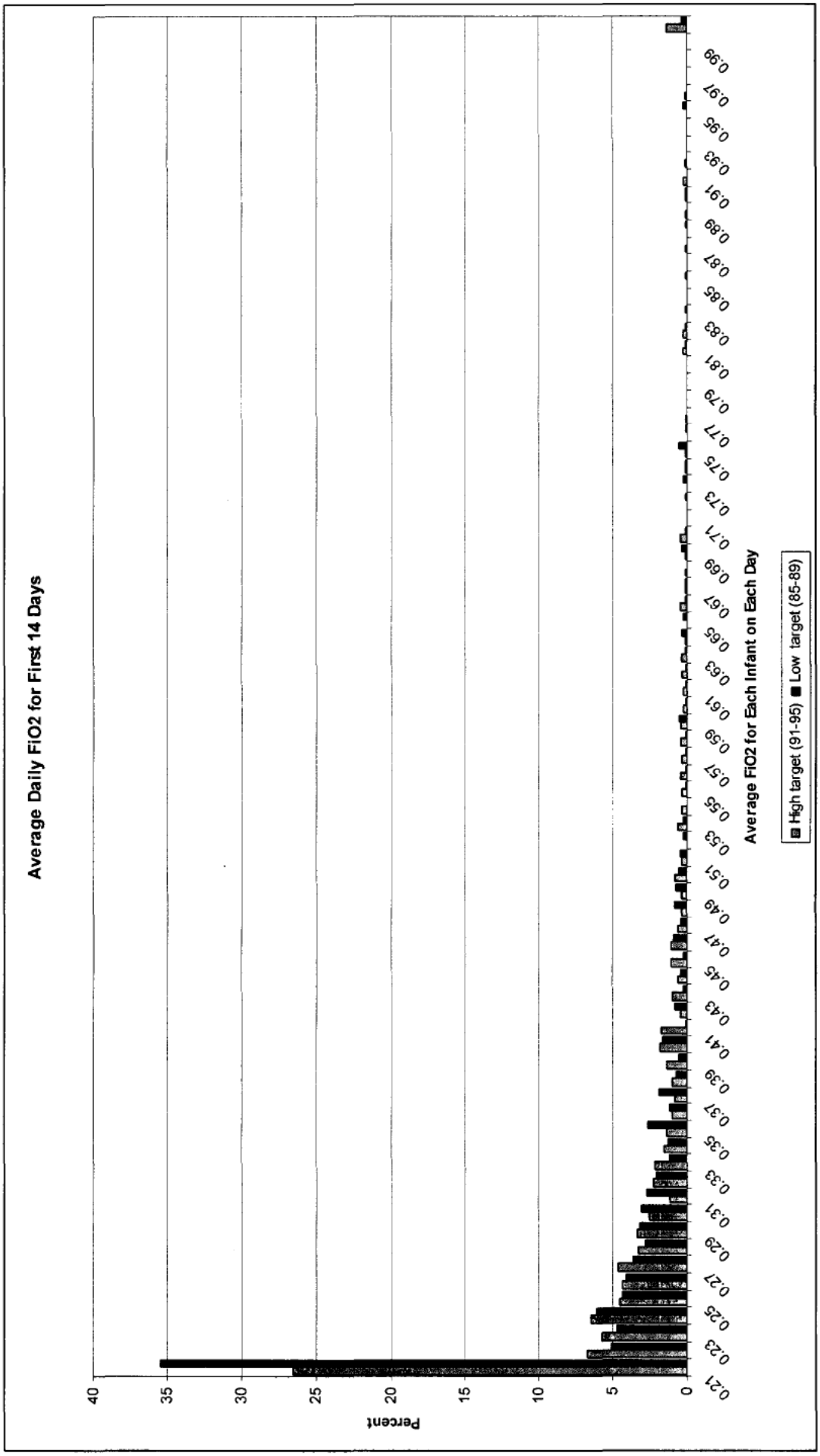
Summary statistics

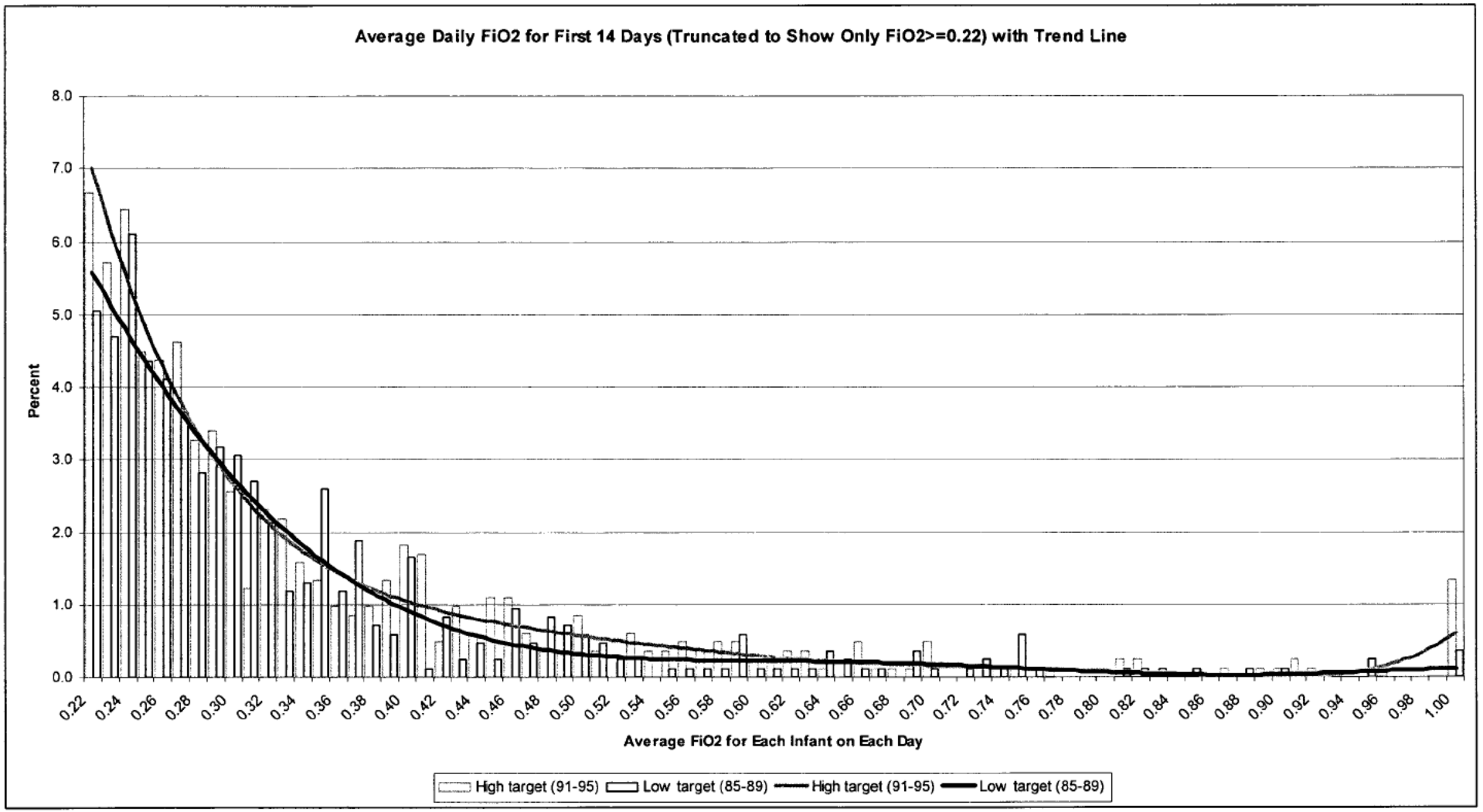
FiO2	High target (91-95)	Low target (85-89)
Mean	0.315	0.294
Maximum	1.000	1.000
90th percentile	0.500	0.447
75th percentile	0.466	0.317
Median	0.260	0.247
25th percentile	0.213	0.210
10th percentile	0.210	0.210
Minimum	0.210	0.210

Full distribution

Daily average FiO2 (interval lower bound)	High target (91-95)		Low target (85-89)	
	Percent	Cumulative	Percent	Cumulative
0.21	26.6	26.6	35.5	35.5
0.22	6.7	33.3	5.1	40.5
0.23	5.7	39.0	4.7	45.2
0.24	6.4	45.4	6.1	51.4
0.25	4.5	49.9	4.3	55.7
0.26	4.4	54.2	4.1	59.8
0.27	4.6	58.9	3.6	63.5
0.28	3.3	62.1	2.8	66.3
0.29	3.4	65.5	3.2	69.4
0.30	2.5	68.1	3.1	72.5
0.31	1.2	69.3	2.7	75.2
0.32	2.3	71.6	2.1	77.3
0.33	2.2	73.8	1.2	78.5
0.34	1.6	75.4	1.3	79.8
0.35	1.3	76.7	2.6	82.4
0.36	1.0	77.7	1.2	83.5
0.37	0.8	78.5	1.9	85.4
0.38	1.0	79.5	0.7	86.1
0.39	1.3	80.8	0.6	86.7
0.40	1.8	82.6	1.6	88.4
0.41	1.7	84.3	0.1	88.5
0.42	0.5	84.8	0.8	89.3
0.43	1.0	85.8	0.2	89.5
0.44	0.6	86.4	0.5	90.0
0.45	1.1	87.5	0.2	90.2
0.46	1.1	88.6	0.9	91.2
0.47	0.6	89.2	0.5	91.7
0.48	0.4	89.6	0.8	92.5
0.49	0.4	89.9	0.7	93.2
0.50	0.8	90.8	0.6	93.8
0.51	0.4	91.1	0.5	94.2

0.52	0.0	91.1	0.2	94.5
0.53	0.6	91.7	0.2	94.7
0.54	0.4	92.1	0.0	94.7
0.55	0.4	92.5	0.1	94.8
0.56	0.5	93.0	0.1	94.9
0.57	0.4	93.3	0.1	95.1
0.58	0.5	93.8	0.1	95.2
0.59	0.5	94.3	0.6	95.8
0.60	0.2	94.5	0.1	95.9
0.61	0.2	94.8	0.1	96.0
0.62	0.4	95.1	0.1	96.1
0.63	0.4	95.5	0.1	96.2
0.64	0.1	95.6	0.4	96.6
0.65	0.0	95.6	0.2	96.8
0.66	0.5	96.1	0.1	96.9
0.67	0.1	96.2	0.1	97.1
0.68	0.1	96.4	0.0	97.1
0.69	0.1	96.5	0.4	97.4
0.70	0.5	97.0	0.1	97.5
0.71	0.0	97.0	0.0	97.5
0.72	0.0	97.0	0.1	97.6
0.73	0.0	97.0	0.2	97.9
0.74	0.1	97.1	0.1	98.0
0.75	0.1	97.2	0.6	98.6
0.76	0.0	97.2	0.1	98.7
0.77	0.1	97.3	0.0	98.7
0.78	0.0	97.3	0.0	98.7
0.79	0.0	97.3	0.0	98.7
0.80	0.0	97.3	0.0	98.7
0.81	0.2	97.6	0.1	98.8
0.82	0.2	97.8	0.1	98.9
0.83	0.0	97.8	0.1	99.1
0.84	0.0	97.8	0.0	99.1
0.85	0.0	97.8	0.1	99.2
0.86	0.0	97.8	0.0	99.2
0.87	0.1	97.9	0.0	99.2
0.88	0.0	97.9	0.1	99.3
0.89	0.1	98.1	0.0	99.3
0.90	0.1	98.2	0.1	99.4
0.91	0.2	98.4	0.0	99.4
0.92	0.1	98.5	0.0	99.4
0.93	0.0	98.5	0.0	99.4
0.94	0.0	98.5	0.0	99.4
0.95	0.0	98.5	0.2	99.6
0.96	0.1	98.7	0.0	99.6
0.97	0.0	98.7	0.0	99.6
0.98	0.0	98.7	0.0	99.6
0.99	0.0	98.7	0.0	99.6
1.00	1.3	100.0	0.4	100.0





Daily FiO2 values for first 14 days of life (FiO2>=0.22 only)
Average daily FiO2 for each infant (average of 3 FiO2 measurements on SUPP05)
Includes data on 148 infants (71 High target, 77 Low target) for whom pulse oximeter data is available 12-5-05

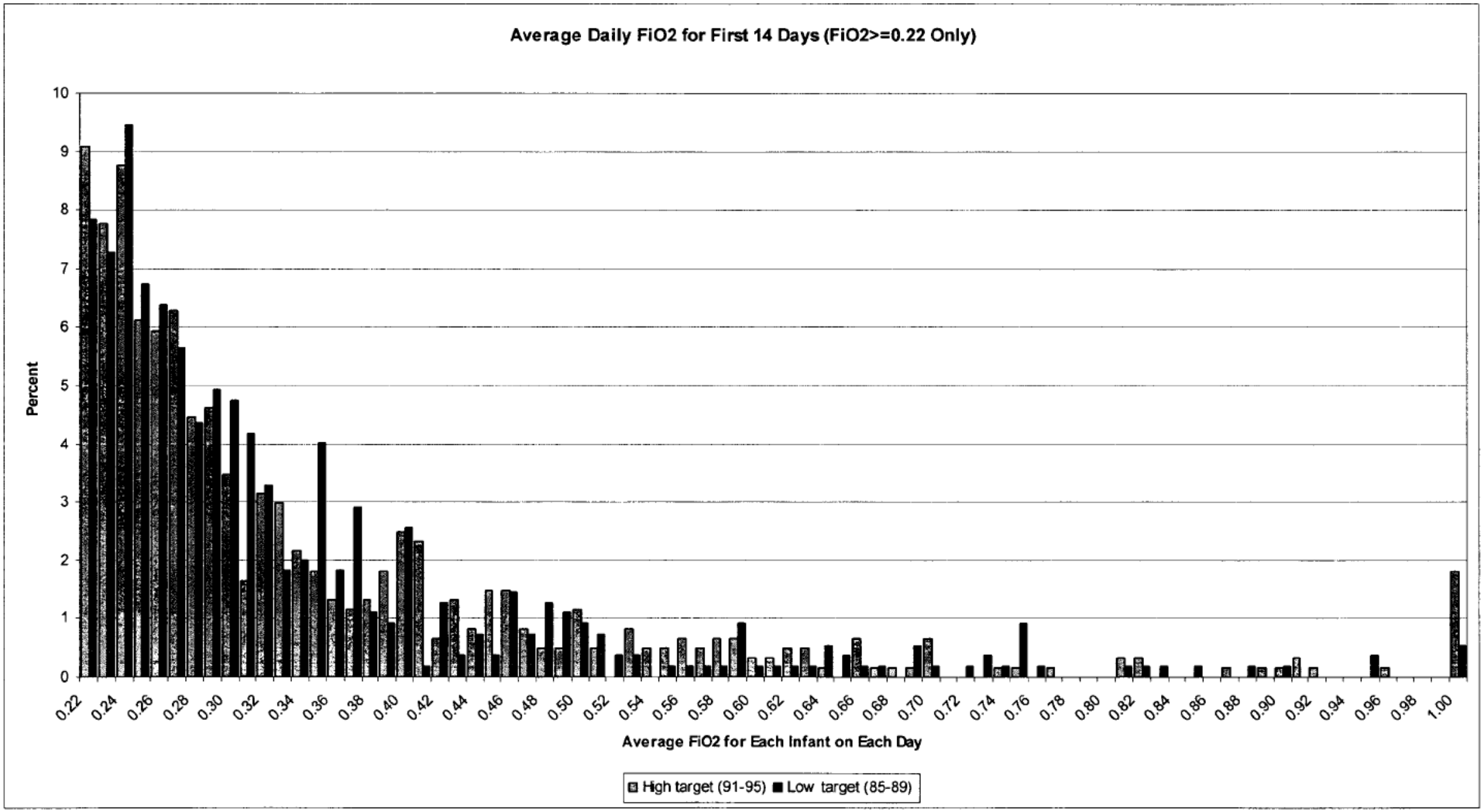
Summary statistics

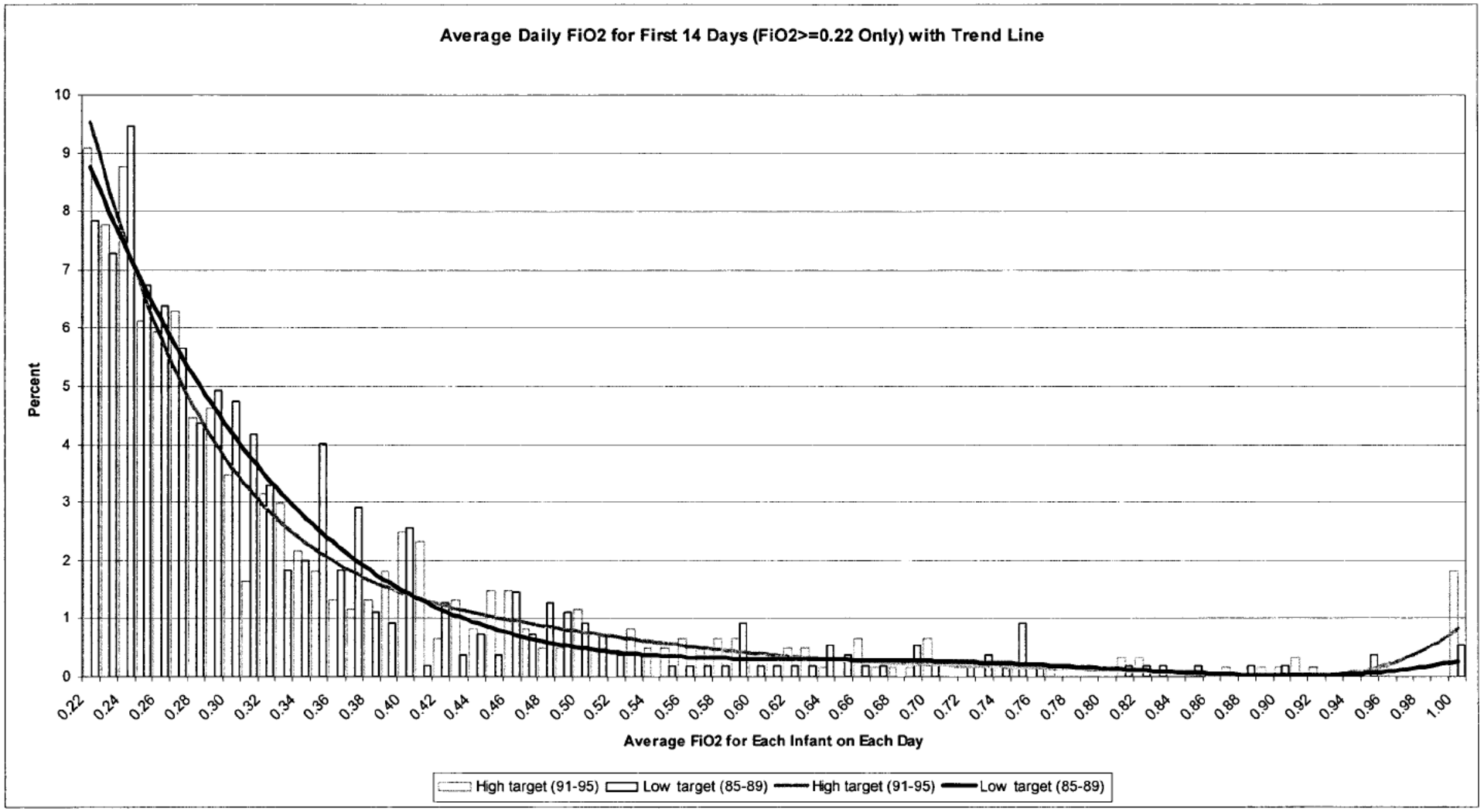
FiO2	High target (91-95)	Low target (85-89)
Mean	0.353	0.340
Maximum	1.000	1.000
90th percentile	0.563	0.503
75th percentile	0.400	0.370
Median	0.290	0.293
25th percentile	0.246	0.250
10th percentile	0.230	0.230
Minimum	0.220	0.220

Full distribution

FiO2	High target (91-95)		Low target (85-89)	
(interval lower bound)	Percent	Cumulative	Percent	Cumulative
0.22	9.09	9.1	7.83	7.8
0.23	7.77	16.9	7.29	15.1
0.24	8.76	25.6	9.47	24.6
0.25	6.12	31.7	6.74	31.3
0.26	5.95	37.7	6.38	37.7
0.27	6.28	44.0	5.65	43.4
0.28	4.46	48.4	4.37	47.7
0.29	4.63	53.1	4.92	52.6
0.30	3.47	56.5	4.74	57.4
0.31	1.65	58.2	4.19	61.6
0.32	3.14	61.3	3.28	64.8
0.33	2.98	64.3	1.82	66.7
0.34	2.15	66.4	2.00	68.7
0.35	1.82	68.3	4.01	72.7
0.36	1.32	69.6	1.82	74.5
0.37	1.16	70.7	2.91	77.4
0.38	1.32	72.1	1.09	78.5
0.39	1.82	73.9	0.91	79.4
0.40	2.48	76.4	2.55	82.0
0.41	2.31	78.7	0.18	82.1
0.42	0.66	79.3	1.28	83.4
0.43	1.32	80.7	0.36	83.8
0.44	0.83	81.5	0.73	84.5
0.45	1.49	83.0	0.36	84.9
0.46	1.49	84.5	1.46	86.3
0.47	0.83	85.3	0.73	87.1
0.48	0.50	85.8	1.28	88.3
0.49	0.50	86.3	1.09	89.4
0.50	1.16	87.4	0.91	90.3
0.51	0.50	87.9	0.73	91.1
0.52	0.00	87.9	0.36	91.4
0.53	0.83	88.8	0.36	91.8
0.54	0.50	89.3	0.00	91.8

0.55	0.50	89.8	0.18	92.0
0.56	0.66	90.4	0.18	92.2
0.57	0.50	90.9	0.18	92.3
0.58	0.66	91.6	0.18	92.5
0.59	0.66	92.2	0.91	93.4
0.60	0.33	92.6	0.18	93.6
0.61	0.33	92.9	0.18	93.8
0.62	0.50	93.4	0.18	94.0
0.63	0.50	93.9	0.18	94.2
0.64	0.17	94.0	0.55	94.7
0.65	0.00	94.0	0.36	95.1
0.66	0.66	94.7	0.18	95.3
0.67	0.17	94.9	0.18	95.4
0.68	0.17	95.0	0.00	95.4
0.69	0.17	95.2	0.55	96.0
0.70	0.66	95.9	0.18	96.2
0.71	0.00	95.9	0.00	96.2
0.72	0.00	95.9	0.18	96.4
0.73	0.00	95.9	0.36	96.7
0.74	0.17	96.0	0.18	96.9
0.75	0.17	96.2	0.91	97.8
0.76	0.00	96.2	0.18	98.0
0.77	0.17	96.4	0.00	98.0
0.78	0.00	96.4	0.00	98.0
0.79	0.00	96.4	0.00	98.0
0.80	0.00	96.4	0.00	98.0
0.81	0.33	96.7	0.18	98.2
0.82	0.33	97.0	0.18	98.4
0.83	0.00	97.0	0.18	98.5
0.84	0.00	97.0	0.00	98.5
0.85	0.00	97.0	0.18	98.7
0.86	0.00	97.0	0.00	98.7
0.87	0.17	97.2	0.00	98.7
0.88	0.00	97.2	0.18	98.9
0.89	0.17	97.4	0.00	98.9
0.90	0.17	97.5	0.18	99.1
0.91	0.33	97.9	0.00	99.1
0.92	0.17	98.0	0.00	99.1
0.93	0.00	98.0	0.00	99.1
0.94	0.00	98.0	0.00	99.1
0.95	0.00	98.0	0.36	99.5
0.96	0.17	98.2	0.00	99.5
0.97	0.00	98.2	0.00	99.5
0.98	0.00	98.2	0.00	99.5
0.99	0.00	98.2	0.00	99.5
1.00	1.82	100.0	0.55	100.0





In response to the comments and concerns of the DSMC, the SUPPORT committee held a conference call Monday Nov 28th at 10:00 to 1130AM to prepare a response. This issue and the preparation of a response was then discussed by the entire NICHD Neonatal Research Network Steering Committee in a conference call held Wednesday. Nov 30th at 9:30 – 11:00 AM. This response has been reviewed by the SUPPORT Subcommittee, and subsequently by the Steering Committee, and reflects the input of all NICHD Principal Investigators.

- The DSMC made the following 2 comments in their letter regarding the SUPPORT trial. This was generated after they reviewed the oximeter data, which was corrected back to actual SpO2 values from the altered values displayed at the bedside:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

We have responded to each of these concerns and our responses are detailed below

Response to Issue Number 1

We appreciate the concern expressed by the DSMC regarding a potential safety issue secondary to durations of SpO2 values greater than 95%.

1. Review of existing evidence and practice regarding durations of higher SpO2 values:

To date there are no prospective data which define the SpO2s experienced by the ELBW infant from birth as part of usual clinical care. Because no published studies have evaluated the effects of different target SpO2 ranges from birth on important outcomes, this was one of the principle reasons for the design and conduct of the SUPPORT trial.

A number of studies have evaluated different alarm limits, but have not reported the actual durations of SpO2 in the various ranges. Nghiem et al in a PAS abstract this year reported that nurses caring for ELBW infants believe that an acceptable oxygen saturation range should include higher upper limits than

specified by current policy (Nghiem et al, Nursing Opinions and Practices of Oxygenation in Prematures: The NOPOP Study PAS #3415, 2005). The study by Hagadorn reported as a late breaker at the PAS last year (Hagadorn et al, Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation. PAS 2004, Attached) did report on the experience of monitoring the actual SpO2 for 72 hours in the first 4 weeks of life in 78 ELBW infants. They reported that the "lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for a median of 70 hours (25th-75th percentiles 67-71 hr) during each of the first 24 weeks. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25th-75th percentiles 91-97%; range of study center medians 91-96%. Centers ranged between 16-71% compliance with their individual intended SpO2 range. Most noncompliance was above intended range." In comparing the SUPPORT data evaluated to date by the DSMC, it is of interest that the mean SpO2 in the 2 Oximeter arms is 90% and 92%, with medians of 92% and 94%, all of which are below that reported by Hagadorn et al (median=95).

The 2 other relevant trials, STOP-ROP and BOOST, both enrolled infants of > 32 weeks postmenstrual age (PMA), and maintained 2 levels of SpO2, 89% to 94% and 91-94% versus 95% to 98% and 96% to 99%, by administration of oxygen. These studies achieved reasonable separation, but did demonstrate substantial overlap of the intended ranges (estimated to be 50% or greater, D Phelps, PI for STOP-ROP). It is important to note that these studies were testing two ranges both of which were higher than the lower range of the SUPPORT trial (85% to 89%) and were treating infants who, for the most part, had recovered from their acute disease. In the BOOST trial 70% of the enrolled infants were < 28 weeks of age at birth (all of SUPPORT is < 28 weeks), 32 weeks PMA, and required oxygen at enrollment (Askie et al, New England Journal of Medicine. 2003; 349(10):959-967). The STOP-ROP trial enrolled infants with pre-threshold ROP at a PMA of 35.4 + 2.5 weeks of age (Phelps et al, Pediatrics. 2000; 105(2):295-310). These trials then gave the higher SpO2 range infants additional oxygen to increase their SpO2 to the desired range. STOP-ROP reported that the infants in the high range had an SpO2 > 95% for > 97% of the monitored time. These studies found an overall increase in pulmonary morbidity in the higher SpO2 range infants.

Examination of oximeter data from one of the NRN sites (Case Western, Walsh et al) obtained for an ongoing study evaluating infants similar to those enrolled in SUPPORT, and managed with conventional oximeters, revealed that for the 9 infants for whom results were available that the percentage of time with and SpO2 > 95% was > 50%.

2. Impact of SUPPORT oximeters algorithm on sat values:

The oximetry algorithm that was designed for the SUPPORT trial is such that re-conversion of the altered oximeter values does not result in a discrete SpO2 number for every displayed value. SpO2 values, of 93%, 94% 95% and 96% will all be reconverted to a single value. As an example, when the actual percent of time at each individual SpO2 point was calculated for this review, in

the 91% to 95% group, there was 5.76% of the time spent at an actual SpO2 of 96% and 8.38% of the time spent at values that represented conversion from readings of 93% to 95%. In the 85% to 89% arm, values of 84%, 85%, 86% and 87% will be reconverted to a single value of 84%. This is a result of having the displayed values return to non-skewed SpO2 values at < 84% and > 96%, a safety design felt to be important by all involved in this trial (See Attached file USCD1). Thus the percentages reported to the DSMC for some of the ranges that include these values were not an accurate representation of the true values. However all values > 96% and < 84% are actual and do not require any conversion.

Percent of time of spent at SpO2 < 84% and > 96%
(RTI, Dec 2, 2005)

Range **Assigned**	High target (91-95)	Low target (85-89)
< 84%	8.30	14.05
> 96%	21.45	15.47

In the current SUPPORT study, an initial analyses utilizing only unaltered SpO2 values as shown above , ie those below 84% and above 96%, have shown that one arm had an SpO2 > 96% for 15.47% versus 21.45% of the time for the comparison arm, and the duration of an SpO2 < 84% was also different at 14.05% versus 8.30%. The values for SpO2s > 96% using unaltered data suggests that the SUPPORT trial to date has, if anything, reduced the duration of higher oxygen saturations.

In addition, analyses using only actual SpO2 demonstrate that the infants in this trial who are receiving supplemental oxygen are spending approximately 70% of the time with a true SpO2 value between 84% and 96%. We believe that this is information is very encouraging.

3. Impact of inclusion of data from periods in room air on saturation distributions:

As part of the SUPPORT trial, we collect information about inhaled oxygen concentration 3 times a day for the first 14 days and daily thereafter. We believe that an improved documentation of the times when infants are on room air will allow us to determine the saturations during actual oxygen exposure. At the present an infant is considered to be receiving supplemental oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized as receiving supplemental oxygen for significant periods when they are actually in room air. This would result in durations of SpO2 greater than 95% that were felt to be modifiable and reported as such when in fact there is no effective treatment for such elevated SpO2s. In addition, we do not know if such SpO2s on room air are associated with any morbidity. From the SUPPORT study data analyses to date we know that infants in room air have SpO2s > 95% for 46% to 69% of the time. By using only information for actual SpO2 values of

96%, we have determined that the infants in the 91%-95% group had a duration at an SpO2 of 96% of 6.68%, and a total duration of 96% or greater of 28.13%.

In view of this design, we would suggest that all future interval analyses for safety examine the ranges of <84% and >96% and consider those ranges for review of low and high durations of SpO2.

We believe that the SUPPORT trial will actually define the periods of time that ELBW infants spend with different ranges of SpO2, and that it is essential to collect this information. In addition, as our findings indicate a lower true percent of the time at SpO2 values >95%, and lower median SpO2 values than has previously been reported, we are in fact, reducing the time with high SpO2 values compared to usual care. The SUPPORT trial carefully evaluates risks, and we will be evaluating group differences for all important short and long term outcomes.

The SUPPORT trial methodology actively encourages all caretakers to keep SpO2 < 96% by having alarm limits set at 85% and 95%. These limits were utilized because it was felt that these represented current practice, and there are no studies which have provided information regarding durations of SpO2 below 85% and subsequent outcomes. While we have had substantial discussion about decreasing the lower alarm limit to below 84%, we are reluctant to make such a recommendation in view of the likely resultant increases in durations of SpO2 below 84%. It is difficult to lower the current high alarm limit of 95% as the 91%-95% group would be alarming when still in target range. The oximetry algorithms were designed to keep infants in the narrower target range of 88% to 92% with the realization that setting alarm limits at these values would severely increase the frequency of the alarms sounding. Nevertheless, our results to date suggest that we have decreased the expected percent of time > 95%, and in one group the value of 14% may be as low as is achievable in an actual clinical environment given the evidence provided by Hagadorn et al and Nghiem et al. In addition a preliminary analysis of the FiO2 exposure of the 2 oximeter groups has demonstrated that the 85% - 89% group have a substantially decreased exposure to oxygen compared to the 91% - 95% group. (See below)

We believe the SUPPORT study will define the distribution and durations of pulse oximetry values among premature infants in highly staffed, dedicated academic centers, and among infants randomized to two different target ranges. For this reason alone, the SUPPORT trial will be very valuable. All of the procedures outlined below in response to your second concern will also allow us to further increase the percentage of time that the infants are in the maximally altered SpO2 ranges which we believe will further increase separation of these groups.

Response to Issue Number 2

There is concern that we have not achieved adequate separation by the current oximeters and study personnel.

1. As described above, the results of additional analyses performed in response to the concerns of the DSMC show differences in the durations of low and high SpO2s between the 2 oximeter groups, but lesser differences in the narrower target ranges. A careful analysis of the most recent converted values demonstrates that the cumulative time spent with an SpO2 of 90% or less is 24.0% (91% - 95%) versus 39.5% (85% - 89%). In addition, the 91% -95% group spend 40% of the time in that narrow range which may represent the achievable target duration for the narrow target range. The 85% - 89% oximeter group spends 18% of the time in their narrow target. One obvious reason for this difference is that when the 91%-95% group exceeds the high end of the range, the oximeter alarms, whereas this does not occur for the high end of the lower range infants.

We have now had an opportunity to review the actual FiO2 exposure of the 2 oximeter groups and that analysis is attached (Daily FiO2 for first 14 days). This analysis has shown that the infants in 85% - 89% group spend approximately 10% more time in room air in the first 14 days than infants in the 91% - 95% group (35.5% vs 26.6%). We do not at the present time have any comparative data for similar populations of ELBW infants, and the actual significance of these differences will only become apparent when the trial is completed.

2. We do acknowledge that it would be desirable to increase the percentage of time in the narrower target range and towards this end would propose the following changes to SUPPORT:

A. We will **change the high alarm to 94% to further assist in keeping the 85%- 89% group more in target and reduce the durations of SpO2 > 95% in the 91% - 95% group**. This change should improve our time in the narrow target ranges and further separate our 2 oximeter groups. For the 91%-95% group, at present when the study oximeter reads greater than 92%, the actual SpO2 is at 95%. This will result in more frequent high alarms for this group, the result of which will be to reduce the durations of higher SpO2s.

B. We will require **documentation that the oximeters alarm limits are set and functional as per protocol every 4-6 hours**. We have found that in some units the high alarms are being turned off, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned to the most appropriate personnel in each unit, which may include bedside or research nurses or respiratory therapists, and this procedure is already being done in many NRN units.

C. We will immediately initiate a **change in our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect saturations measured while on oxygen therapy and exclude saturations of infants in room air.** We will change the data form to indicate that the infant was either in oxygen for the entire 24 hours, and if not, will provide a more accurate estimate of the true time in oxygen, and we will continue with this form of data collection for the entire time that the infant is receiving oxygen. In the current protocol we

collect such information 3 times a day for the first 14 days only and then daily thereafter. We believe that more frequent and extended documentation will allow us to determine more accurately the actual time that an infant is in room air. At the present the infant is considered to have spent a day in oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized in oxygen for significant periods when they are in room air. While in room air, we cannot manipulate the SpO2, and thus knowledge of the true time in oxygen will produce a more accurate representation of oximetry results that are subject to care interventions.

D. We will initiate **further training and in-service, and a change to the protocol to stress the importance of keeping the SpO2 alarms functional and at the limits of 85% and 94%**. In the past these were guidelines, and we will now change the study manual and protocol to indicate these limits are now set by protocol and that violations will be documented. We will encourage all caretakers to aim for an SpO2 value of 90% and make every effort to educate caretakers to make smaller adjustments in FiO2 and ensure that the infant is maintained between the 87% to 93%, the range with the maximal separation of the study oximeters. We will further facilitate the use of the 2 hour and 12 hour histograms showing the infants' actual ranges to provide feedback to the caretakers regarding the percentage of time in the target ranges.

E. We will develop **guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation**. More modulated increases in oxygen during these desaturation events will minimize overshoot and the potential of high SpO2 values. We would hope that such changes – ie increasing the FiO2 in steps of 5% as opposed to much larger increases will decrease the resultant overshoots creating the high SpO2 values. This will be included in the revised manual of operations.

F. **We will place bedside cards to indicate the desired target range**.

G. We will **initiate compliance monitoring visits coordinated by RTI to visit random sites**. These visits had been planned, but had not yet been initiated. The teams will consist of a member of RTI and a study coordinator, and they will review the adherence to the protocol and any other relevant issues.

H. We would recommend that at a minimum, **the unblinded oximetry data be reviewed again after an additional 100 to 150 infants have been enrolled in this trial.**

We thank the DSMC for their thoughtful concerns. We trust that our plans to move forward with the SUPPORT trial are acceptable to the DSMC. We are anxious to initiate the above changes, seek IRB approvals and re-activate this trial.

UNIVERSITY OF CALIFORNIA, SAN DIEGO UCSD

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatology
Department of Pediatrics

Medical Center – Hillcrest
200 West Arbor Drive
San Diego, CA 92103-8774
(619) 543-3759
Fax (619) 543-3812

December 05, 2005

Gordon Avery, M.D.
Chairman of the Data Safety Monitoring Committee
NICHD Neonatal Research Network

Dear Dr. Avery,

The SUPPORT Trial Subcommittee and the NICHD Network Steering Committee have reviewed in detail the concerns of the Data Safety Monitoring Committee. We are appreciative of the diligence and thoughtfulness that went into these concerns and we have carefully considered the comments made by the Data Safety Monitoring Committee with respect to both the issue of patient safety and the question of futility relative to the separation of the infants in the two oximetry arms of the trial.

We are very mindful of the need to protect patient safety and toward this end have reviewed the current experience relative to exposure of current ELBW infants to saturations above 95%. There is little information regarding this issue in the literature. We have quoted what we believe to be the relevant recent experiences, including the Network experience with exposures to higher SpO2 ranges. In addition we had asked RTI to provide us with unaltered oximetry data which allows us to look at information for oxygen saturations of 97% or greater and less than 84%, as these values were not altered by the algorithm in place for the study. We also compared the mean and median values of the SpO2 seen in the SUPPORT trial to date with those reported by Hagadorn et al, the only other report that contains such information. This information suggests that our current SpO2 exposures, especially to SpO2 values of 97% and above, for infants within the SUPPORT trial are probably less than is currently being experience outside of the trial, both from the Network experience and in the general practice of neonatology for the ELBW infant. In addition our median SpO2 values for both of our oximetry groups are lower than those reported by Hagadorn et al. An initial evaluation of the FiO2 data does demonstrate that the 85%-89% group requires oxygen for 10% less overall duration than the 91%-95% group, further indicating that these groups are being separated in their clinical management.

We agree that we should aim for greater separation between the oximetry groups, and are pleased that we are seeing some differences on SpO2 and FiO2 exposures between the groups. There is less separation in the target ranges than we desired, and I have detailed our responses to each of the DSMC's concerns in the attached review. We believe that with these changes to the Protocol and Manual of operations and additional in-service at the sites coupled with intermittent site visits, that we will attain an even greater SpO2 separation in all ranges, and differential oxygen exposure for our 2

study groups. We would also like to recommend a re-evaluation of this data after an additional 100-150 infants have been enrolled.

We thank you and your committee for your careful review and suggestions. We hope that our responses are appropriate and that we may be allowed to continue this important trial

Sincerely,

Neil N. Finer, M.D.
Principal Investigator on behalf of the SUPPORT Subcommittee

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Trial
Date: Monday, December 05, 2005 10:22:11 AM

Thanks Rose
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, December 05, 2005 6:26 AM
To: nfiner@ucsd.edu
Subject: Re: SUPPORT Trial

Neil
I checked on this and will compose a few lines that are acceptable to NICHD that can be made public - for now, refer them to me.
Thanks for making me aware of this.

Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Sun Dec 04 22:17:45 2005
Subject: FW: SUPPORT Trial

Hi Rose
I received this email today. I will not discuss the trial with anyone outside the study until we have a final decision about moving ahead.
Any thoughts?
Neil

-----Original Message-----
From: ccole@bidmc.harvard.edu [mailto:ccole@bidmc.harvard.edu]
Sent: Sunday, December 04, 2005 3:56 PM
To: nfiner@ucsd.edu
Subject: SUPPORT Trial
Importance: High

Dear Neil,
I realize am not up on the progress of SUPPORT.
The comment from Augusta (in the email below) is very important.
If you do not mind sharing, and if Augusta's comment is true, I would like to learn what issues put SUPPORT on hold, and if the issues are relevant to US POST, BOOST, etc.
I am in Wash DC.
Email you have.
Cell: 617-529(b) (6).
I hope you are well.
Look forward to speaking with you.

- Cindy

-----Original Message-----
From: Augusto Sola [mailto:augusto_sola@oz.ped.emory.edu]
Sent: Saturday, December 03, 2005 5:31 PM
To: Maribeth Sayre
Cc: Valerie Begnoche; """" <ccole@bidmc.harvard.edu>,"Roger.Wu"
<RWu@masimo.com>, "Joe.Kiani" <kiani@masimo.com>,"Mike.Petterson"
<MPetters@masimo.com>"@virginia.cc.emory.edu
Subject: Re: Masimo Holiday Card

Of course my study can be referenced if done appropriately.
SUPPORT has already been put on hold due to poor design (as suggested)
Thank you
Augusto
Maribeth Sayre <MSayre@masimo.com> on Friday, December 02, 2005 at 2:39
PM
+0000 wrote:
>Hi Valerie,
>
>Since the SUPPORT and BOOST II studies are just getting underway, and
we
>will not have information about the outcomes of these studies for
several
>years, I would suggest we NOT reference ROP on our cards at this time.
>
>Maribeth
>
>
>-----Original Message-----
>From: Valerie Begnoche
>Sent: Friday, December 02, 2005 10:02 AM
>To: 'ccole@bidmc.harvard.edu'; 'augusto_sola@oz.ped.emory.edu';
Maribeth
>Sayre
>Cc: Roger Wu
>Subject: Masimo Holiday Card
>
>
>Dear Colleagues:
>Masimo is considering including a message in our holiday card that
makes
>reference to Dr. Sola's study on ROP. Please let us know if you have
any
>concerns or objections about the message.
>
>Regards,
>Valerie Begnoche
>for Joe Kiani
>

From: Spong, Catherine (NIH/NICHD)
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT Trial
Date: Monday, December 05, 2005 9:09:40 AM

You can but (b) (5) [redacted] it...but if you want, feel free

Catherine Y Spong MD
Chief, Pregnancy and Perinatology Branch, NICHD, NIH
6100 Executive Blvd, Rm 4B03, MSC 7510
Bethesda MD 20892 (express mail: Rockville MD 20852)
Phone 301 435 6894 or 301 496 5575
Fax 301 496 3790
email spongc@mail.nih.gov

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From: Higgins, Rosemary (NIH/NICHD)
Sent: Monday, December 05, 2005 9:09 AM
To: Spong, Catherine (NIH/NICHD)
Subject: Re: SUPPORT Trial

Perhaps we should (b) (5) [redacted] - that would likely work.

Thabks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Spong, Catherine (NIH/NICHD) <spongc@dir49.nichd.nih.gov>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Mon Dec 05 09:03:46 2005
Subject: RE: SUPPORT Trial

I would suggest (b) (5) [redacted]
Something along those lines...does that work?

Catherine Y Spong MD
Chief, Pregnancy and Perinatology Branch, NICHD, NIH
6100 Executive Blvd, Rm 4B03, MSC 7510
Bethesda MD 20892 (express mail: Rockville MD 20852)
Phone 301 435 6894 or 301 496 5575
Fax 301 496 3790
email spongc@mail.nih.gov
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Sent: Sunday, December 04, 2005 10:56 PM
To: Spong, Catherine (NIH/NICHD)
Subject: Fw: SUPPORT Trial
Importance: High

Cathy -
See email below - Augusta Sola is the chief of neonatology at Emory. Cynthia Cole, as you know, is organizing POST ROP. (b) (5) [redacted]

Thanks

Rose

Sent from my BlackBerry Wireless Handheld

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>Regards,
>Valerie Begnoche
>for Joe Kiani
>

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD) [E]; "Avroy A. Fanaroff, M.D."; "Betty Hastings"; Das, Abhik; "Ed Donovan"; "Ken Poole"; Maynard Rasmussen; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Date:	Sunday, December 04, 2005 10:53:21 PM
Attachments:	SUPPORT Trial DSMC Response.ppt Response to DSMC Steering Final2 Dec4.doc

Hi Rose and Everyone

I have asked Marie to do some analyses for FiO2. I think that our response as written in the attached revision - - Dec 4 – is the one that should go forward to the DSMC

I prepared a PowerPoint presentation. Once we see the FiO2 data, we can decide how or if to use them. I would like your opinions as to whether I should use this with the DSMC during the phone call by circulating it to them in advance.

I will be on service this week but will keep close to the email and phone.

Be well

Neil

SUPPORT Trial
Response to the DSMC

December 3 2005

Report of the DSMC Nov 2005

The DSMC expressed 2 concerns:

1. **There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range**

Report of the DSMC Nov 2005

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Response to DSMC

Safety Issue of SpO2>95%

Concern regarding safety issue of duration of SpO2 > 95%

- ✓ **The current best data from Hagadorn et al evaluated 78 ELBW infants for 70 hours per week for the first 4 weeks of life**
- ✓ **Lower and upper limits were 83% -92% and 92%-98%**
- ✓ **Median SpO2 = 95%**
- ✓ **Medians from SUPPORT Oximeter groups – 92% and 94%**

Response to DSMC:
Safety Issue of SpO2>95%

- STOP-ROP high treatment infants spent 97% of time > 95%
- Case Western a current NRN Center – Current data from SUPPORT type ELBW infants – SpO2 > 95% for > 50% time
- SUPPPORT Infants on room air – SpO2 > 95% from 46% to 69% of time

Response to DSMC: Safety Issue of SpO2>95%

- **The actual algorithm for conversion of displayed versus actual values results in inability to create a whole value for each displayed value.**
- **We calculated the time that infants were > 96%**

  and < 84%
- **These values may be the first such data for a large group of ELBW infants that has been reported.**
- **These values appear lower than any previous reports**

Response to DSMC: Safety Issue of SpO2>95%

Percent of time of spent at SpO2 < 84% and > 96% (RTI, Dec 2, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.30%	14.05%
> 96%	21.45%	15.47%

Response to DSMC: Safety Issue of SpO2>95%

- **We believe that neither oximeter group in the SUPPORT trial is being exposed to excessive durations of SpO2 > 95% based on all currently available information and the actual SUPPORT Trial Data analyzed to date.**
- **Current analyses demonstrate that the highest duration of SpO2 > 95% was 28.13%, the lowest value that we believe has been reported for any group of preterm infants.**

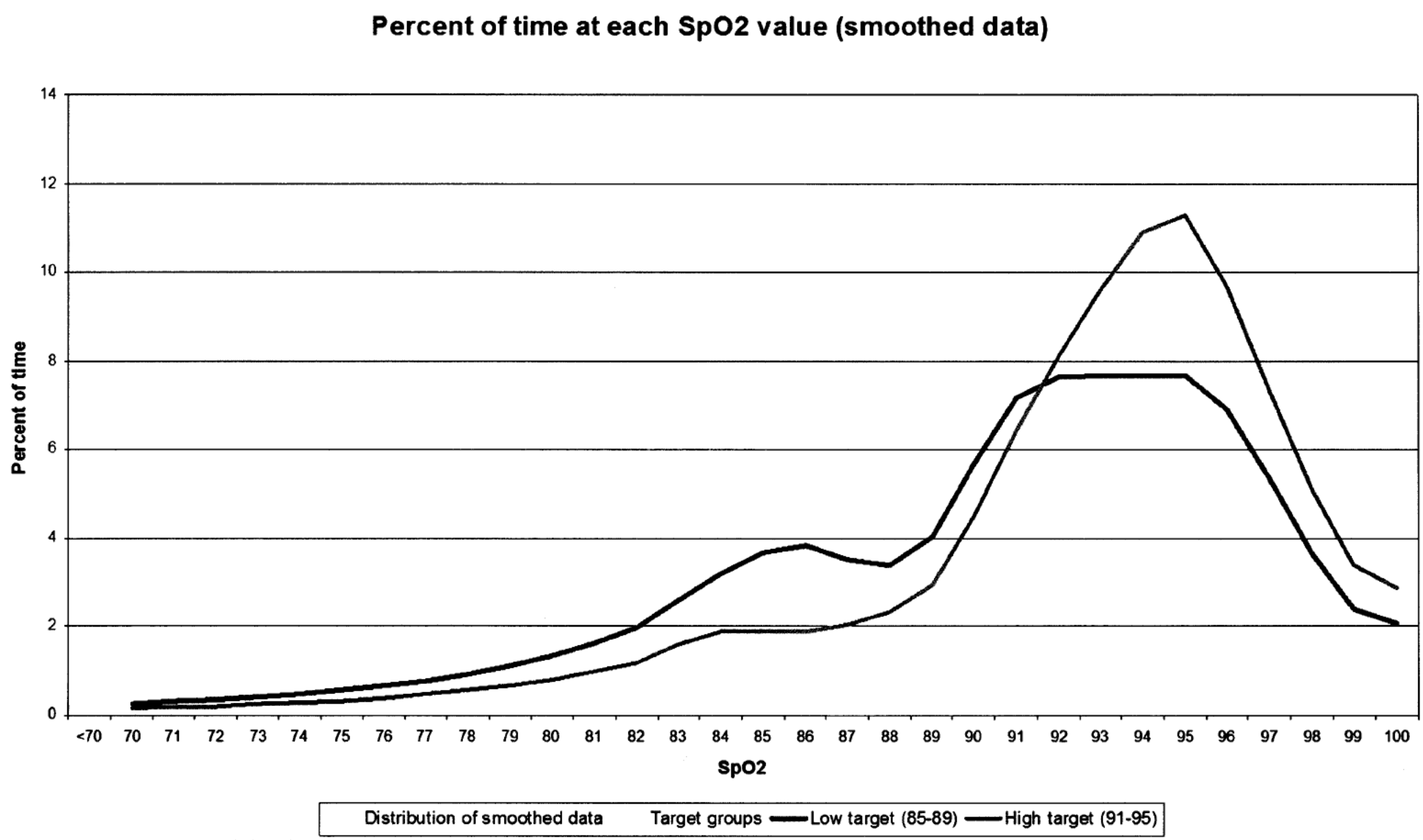
Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **An evaluation of the oximeter group data has revealed that there is a difference in the mean - 90% vs 92% and median values for the 2 groups – 92% vs 94%**
- **In additional analyses have demonstrated that the cumulative time spent with an SpO2 of 90% or less is 24.0% (91% - 95%) versus 39.5% (85% - 89%) for a > 15% difference between the groups**

Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **Further evaluation of the data analyzed in response to the concerns of the DSMC have shown the previously described differences for SpO2 values of < 84% and > 97% for the 2 oximeter groups**

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.30%	14.05%
> 96%	21.45%	15.47%



Response to DSMC:
Futility regarding Separation of Oximeter Groups

- **It is uncertain what duration of differences will be associated with different short and long term outcomes, but we are achieving some separation to the present.**
- **We believe that greater separation is possible and have made a number of recommendations to ensure that this will occur**

Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups

1. **Require documentation that the oximeters alarm limits are set and functional as per protocol every 4-6 hours**
2. **Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect saturations measured while on oxygen therapy and exclude saturations of infants in room air**

Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups

3. Further training and in-service at all the sites to stress the importance of keeping the SpO2 alarms functional and at the limits of 85% and 95%.
4. Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation
5. Place bedside cards to indicate the desired target range

Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups

6. **Initiate compliance monitoring visits coordinated by RTI to visit random sites**
7. **Reanalyze group differences after an additional 100-150 infants have been enrolled.**

In response to the comments and concerns of the DSMC, the SUPPORT committee held a conference call Monday Nov 28th at 10:00 to 1130AM to prepare a response. This issue and the preparation of a response was then discussed by the entire NICHD Neonatal Research Network Steering Committee in a conference call held Wednesday. Nov 30th at 9:30 – 11:00 AM. This response has been reviewed by the SUPPORT Subcommittee, and subsequently by the Steering Committee, and reflects the input of all NICHD Principal Investigators.

- The DSMC made the following 2 comments in their letter regarding the SUPPORT trial. This was generated after they reviewed the oximeter data, which was corrected back to actual SpO2 values from the altered values displayed at the bedside:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

We have responded to each of these concerns and our responses are detailed below

Response to Issue Number 1

We appreciate the concern expressed by the DSMC regarding a potential safety issue secondary to durations of SpO2 values greater than 95%.

1. Review of existing evidence and practice regarding durations of higher SpO2 values:

To date there are no prospective data which define the SpO2s experienced by the ELBW infant from birth as part of usual clinical care. Because no published studies have evaluated the effects of different target SpO2 ranges from birth on important outcomes, this was one of the principle reasons for the design and conduct of the SUPPORT trial.

A number of studies have evaluated different alarm limits, but have not reported the actual durations of SpO2 in the various ranges. Nghiem et al in a PAS abstract this year reported that nurses caring for ELBW infants believe that an acceptable oxygen saturation range should include higher upper limits than

specified by current policy (Nghiem et al, Nursing Opinions and Practices of Oxygenation in Prematures: The NOPOP Study PAS #3415, 2005). The study by Hagadorn reported as a late breaker at the PAS last year (Hagadorn et al, Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation. PAS 2004, Attached) did report on the experience of monitoring the actual SpO2 for 72 hours in the first 4 weeks of life in 78 ELBW infants. They reported that the "lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for a median of 70 hours (25th-75th percentiles 67-71 hr) during each of the first 24 weeks. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25th-75th percentiles 91-97%; range of study center medians 91-96%. Centers ranged between 16-71% compliance with their individual intended SpO2 range. Most noncompliance was above intended range." In comparing the SUPPORT data evaluated to date by the DSMC, it is of interest that the mean SpO2 in the 2 Oximeter arms is 90% and 92%, with medians of 92% and 94%, all of which are below that reported by Hagadorn et al (median=95).

The 2 other relevant trials, STOP-ROP and BOOST, both enrolled infants of > 32 weeks postmenstrual age (PMA), and maintained 2 levels of SpO2, 89% to 94% and 91-94% versus 95% to 98% and 96% to 99%, by administration of oxygen. These studies achieved reasonable separation, but did demonstrate substantial overlap of the intended ranges (estimated to be 50% or greater, D Phelps, PI for STOP-ROP). It is important to note that these studies were testing two ranges both of which were higher than the lower range of the SUPPORT trial (85% to 89%) and were treating infants who, for the most part, had recovered from their acute disease. In the BOOST trial 70% of the enrolled infants were < 28 weeks of age at birth (all of SUPPORT is < 28 weeks), 32 weeks PMA, and required oxygen at enrollment (Askie et al, New England Journal of Medicine. 2003; 349(10):959-967). The STOP-ROP trial enrolled infants with pre-threshold ROP at a PMA of 35.4 + 2.5 weeks of age (Phelps et al, Pediatrics. 2000; 105(2):295-310). These trials then gave the higher SpO2 range infants additional oxygen to increase their SpO2 to the desired range. STOP-ROP reported that the infants in the high range had an SpO2 > 95% for > 97% of the monitored time. These studies found an overall increase in pulmonary morbidity in the higher SpO2 range infants.

Examination of oximeter data from one of the NRN sites (Case Western, Walsh et al) obtained for an ongoing study evaluating infants similar to those enrolled in SUPPORT, and managed with conventional oximeters, revealed that for the 9 infants for whom results were available that the percentage of time with and SpO2 > 95% was > 50%.

2. Impact of SUPPORT oximeters algorithm on sat values:

The oximetry algorithm that was designed for the SUPPORT trial is such that re-conversion of the altered oximeter values does not result in a discrete SpO2 number for every displayed value. SpO2 values, of 93%, 94% 95% and 96% will all be reconverted to a single value. As an example, when the actual percent of time at each individual SpO2 point was calculated for this review, in

the 91% to 95% group, there was 5.76% of the time spent at an actual SpO2 of 96% and 8.38% of the time spent at values that represented conversion from readings of 93% to 95%. In the 85% to 89% arm, values of 84%, 85%, 86% and 87% will be reconverted to a single value of 84%. This is a result of having the displayed values return to non-skewed SpO2 values at < 84% and > 96%, a safety design felt to be important by all involved in this trial (See Attached file USCD1). Thus the percentages reported to the DSMC for some of the ranges that include these values were not an accurate representation of the true values. However all values > 96% and < 84% are actual and do not require any conversion.

Percent of time of spent at SpO2 < 84% and > 96%
(RTI, Dec 2, 2005)

Range **Assigned**	High target (91-95)	Low target (85-89)
< 84%	8.30	14.05
> 96%	21.45	15.47

In the current SUPPORT study, an initial analyses utilizing only unaltered SpO2 values as shown above , ie those below 84% and above 96%, have shown that one arm had an SpO2 > 96% for 15.47% versus 21.45% of the time for the comparison arm, and the duration of an SpO2 < 84% was also different at 14.05% versus 8.30%. The values for SpO2s > 96% using unaltered data suggests that the SUPPORT trial to date has, if anything, reduced the duration of higher oxygen saturations.

In addition, analyses using only actual SpO2 demonstrate that the infants in this trial who are receiving supplemental oxygen are spending approximately 70% of the time with a true SpO2 value between 84% and 96%. We believe that this is information is very encouraging.

3. Impact of inclusion of data from periods in room air on saturation distributions:

As part of the SUPPORT trial, we collect information about inhaled oxygen concentration 3 times a day for the first 14 days and daily thereafter. We believe that an improved documentation of the times when infants are on room air will allow us to determine the saturations during actual oxygen exposure. At the present an infant is considered to be receiving supplemental oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized as receiving supplemental oxygen for significant periods when they are actually in room air. This would result in durations of SpO2 greater than 95% that were felt to be modifiable and reported as such when in fact there is no effective treatment for such elevated SpO2s. In addition, we do not know if such SpO2s on room air are associated with any morbidity. From the SUPPORT study data analyses to date we know that infants in room air have SpO2s > 95% for 46% to 69% of the time. By using only information for actual SpO2 values of

96%, we have determined that the infants in the 91%-95% group had a duration at an SpO2 of 96% of 6.68%, and a total duration of 96% or greater of 28.13%.

In view of this design, we would suggest that all future interval analyses for safety examine the ranges of <84% and >96% and consider those ranges for review of low and high durations of SpO2..

We believe that the SUPPORT trial will actually define the periods of time that ELBW infants spend with different ranges of SpO2, and that it is essential to collect this information. In addition, as our findings indicate a lower true percent of the time at SpO2 values >95%, and lower median SpO2 values than has previously been reported, we are in fact, reducing the time with high SpO2 values compared to usual care. The SUPPORT trial carefully evaluates risks, and we will be evaluating group differences for all important short and long term outcomes.

The SUPPORT trial methodology actively encourages all caretakers to keep SpO2 < 96% by having alarm limits set at 85% and 95%. These limits were utilized because it was felt that these represented current practice. The oximetry algorithms were designed to keep infants in the narrower target range of 88% to 92% with the realization that setting alarm limits at these values would severely increase the frequency of the alarms sounding. Nevertheless, our results to date suggest that we have decreased the expected percent of time > 95%, and in one group the value of 14% may be as low as is achievable in an actual clinical environment given the evidence provided by Hagadorn et al and Nghiem et al.

We believe the SUPPORT study will define the distribution and durations of pulse oximetry values among premature infants in highly staffed, dedicated academic centers, and among infants randomized to two different target ranges. For this reason alone, the SUPPORT trial will be very valuable. All of the procedures outlined below in response to your second concern will also allow us to further increase the percentage of time that the infants are in the maximally altered SpO2 ranges which we believe will further increase separation of these groups.

Response to Issue Number 2

There is concern that we have not achieved adequate separation by the current oximeters and study personnel.

1. As described above, the results of additional analyses performed in response to the concerns of the DSMC show differences in the durations of low and high SpO2s between the 2 oximeter groups. A careful analysis of the most recent converted values demonstrates that the cumulative time spent with an SpO2 of 90% or less is 24.0% (91% - 95%) versus 39.5% (85% - 89%), for the 2 oximeter groups, supporting the ability of the altered oximeters to produce differential SpO2 exposures.

2. We do acknowledge that it would be desirable to increase the percentage of time in the narrower target range and towards this end would propose the following changes to SUPPORT:

A. We will require **documentation that the oximeters alarm limits are set and functional as per protocol every 4-6 hours**. We have found that in some units the high alarms are being turned off, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned to the most appropriate personnel in each unit, which may include bedside or research nurses or respiratory therapists, and this procedure is already being done in many NRN units.

B. We will immediately initiate a **change in our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect saturations measured while on oxygen therapy and exclude saturations of infants in room air.** We will change the data form to indicate that the infant was either in oxygen for the entire 24 hours, and if not, will provide a more accurate estimate of the true time in oxygen, and we will continue with this form of data collection for the entire time that the infant is receiving oxygen. In the current protocol we collect such information 3 times a day for the first 14 days only and then daily thereafter. We believe that more frequent and extended documentation will allow us to determine more accurately the actual time that an infant is in room air. At the present the infant is considered to have spent a day in oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized in oxygen for significant periods when they are in room air. While in room air, we cannot manipulate the SpO2, and thus knowledge of the true time in oxygen will produce a more accurate representation of oximetry results that are subject to care interventions.

C. We will initiate **further training and in-service at all the sites to stress the importance of keeping the SpO2 alarms functional and at the limits of 85% and 95%**. In the past these were guidelines, and we will now change the study manual and protocol to indicate these limits are now set by protocol and that violations will be documented. We will encourage all caretakers to aim for an SpO2 value of 90% and make every effort to educate caretakers to make smaller adjustments in FiO2 and ensure that the infant is maintained between the 87% to 93%, the range with the maximal separation of the study oximeters. We will further facilitate the use of the 2 hour and 12 hour histograms showing the infants' actual ranges to provide feedback to the caretakers regarding the percentage of time in the target ranges.

D. We will develop **guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation**. More modulated increases in oxygen during these desaturation events will minimize overshoot and the potential of high SpO2 values. We would hope that such changes – ie increasing the FiO2 in steps of 5% as opposed to much larger increases will

decrease the resultant overshoots creating the high SpO2 values. This will be included in the revised manual of operations.

E. We will place bedside cards to indicate the desired target range.

F. We will **initiate compliance monitoring visits coordinated by RTI to visit random sites**. These visits had been planned, but had not yet been initiated. The teams will consist of a member of RTI and a study coordinator, and they will review the adherence to the protocol and any other relevant issues.

G. We would recommend that at a minimum, **the unblinded oximetry data be reviewed again after an additional 100 to 150 infants have been enrolled in this trial.**

We thank the DSMC for their thoughtful concerns. We trust that our plans to move forward with the SUPPORT trial are acceptable to the DSMC. We are anxious to initiate the above changes, seek IRB approvals and re-activate this trial.

From:	Neil Finer
To:	"Phelps, Dale"; "D"Angio, Carl"; Higgins, Rosemary (NIH/NICHD) [E]; alaptook@WIHRI.org; ""Abhik Das" "; ""Brenda Poindexter" "; ""Carlo Waldemar (E-mail)" "; ""Charles Rosenfeld" "; ""Ed Donovan" "; ""Ehrenkranz Richard (E-mail)" "; ""Jobe Alan (E-mail)" "; ""Lemons Jim (E-mail)" "; ""Michael O"Shea" "; ""Michelle Walsh" "; ""Oh William (E-mail)" "; ""Poole Kenneth (E-mail)" "; ""Ronald GOldberg" "; ""Shahnaz Duara" "; ""Shankaran Seetha (E-mail)" "; ""Stevenson David (E-mail)" "; ""Stoll Barbara (E-mail)" "; ""Tyson Jon (E-mail)" "; walid.salhab@utsouthwestern.edu
Cc:	"Laroia, Nirupama"; vanmeurs@stanford.edu; ""Avroy A. Fanaroff" "; reverett@med.miami.edu; kurt.schibler@cchmc.org; ambal@uab.edu; ""Morris, Brenda H" "; ""Michael Cotten" "; "Wade Rich "; ""Gantz, Marie" "; ""Petrie, Carolyn" "; "Gantz, Marie"
Subject:	RE: More thoughts about are the groups separated
Date:	Sunday, December 04, 2005 11:21:40 AM
Attachments:	Analyses of each hour with graphs.doc

Hi Dale
Thanks for these suggestions.
You have provided us with some very good ideas. I will be talking with RTI to see how quickly such analyses could be performed. We have demonstrated from the analyses at present that there is some separation between the 2 oximeter groups, both by the difference in median SpO2, and the durations of SpO2 > 97% and < 84%. We need to get our response to the DSMC so that they can have a reasonable time to review these.
I will prepare some additional information based in FiO2 analyses using your approach, and be prepared to present these.
I think that we have dealt with the issues that have been raised, and I fear that if we don't have adequate FiO2 differences based on 150 infants, that this may be used to stop this arm.
Marie Gantz has provided some further data looking at the time at each SpO2 value with smoothed curves and histograms which I think are useful. I think that these address some of your thoughts re STOP-ROP
I have attached these for everyone to see.
Please pass on my thanks to the entire Rochester Group.
Be well
Neil

-----Original Message-----
From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Saturday, December 03, 2005 12:43 PM
To: 'Neil Finer '; D'Angio, Carl; "Higgins, Rosemary (NIH/NICHD)' '; 'alaptook@WIHRI.org '; "Abhik Das' '; "Brenda Poindexter' '; "Carlo Waldemar (E-mail)' '; "Charles Rosenfeld' '; "Ed Donovan' '; "Ehrenkranz Richard (E-mail)' '; "Jobe Alan (E-mail)' '; "Lemons Jim (E-mail)' '; "Michael O'Shea' '; "Michelle Walsh' '; "Oh William (E-mail)' '; "Poole Kenneth (E-mail)' '; "Ronald GOldberg' '; "Shahnaz Duara' '; "Shankaran Seetha (E-mail)' '; "Stevenson David (E-mail)' '; "Stoll Barbara (E-mail)' '; "Tyson Jon (E-mail)' '; 'walid.salhab@utsouthwestern.edu '
Cc: Laroia, Nirupama; 'vanmeurs@stanford.edu '; "Avroy A. Fanaroff' '; 'reverett@med.miami.edu '; 'kurt.schibler@cchmc.org '; 'ambal@uab.edu '; "Morris, Brenda H' '; "Michael Cotten' '; 'Wade Rich '; "Gantz, Marie' '; "Petrie, Carolyn' '
Subject: RE: More thoughts about are the groups separated

Neil,

Our group discussed the SUPPORT suspension and the rationale for it and the responses on Friday.

On the issue of "is there any real separation of the two groups", we had two additional thoughts.

1) Direct data: a frequency histogram of saturations (during modifiable time) can be prepared with 'accurate' saturations. When the numbers looked 'too similar' to the DSMC for STOP-ROP, (lack of separation), they found the histograms to be persuasive.

a. The 'real' saturations should be available since you have the 86.5, 85.75 etc. data from the downloads. It is a matter of time and computing to do it.

b. If you want to save time for RTI, you could limit the amount of time from one infant that is analyzed by limiting it to just the first 2 weeks... or first 4 weeks?

c. You won't be able to get the really clean modifiable data until the data forms are changed. (a hitch)

2) Indirect data: Since you have a lot of kids (153), and thereare data for the first 14 days on FiO2 at three points in time on each of those first 14 days, you should be able to look at the "area under the curve" for the oxygen exposure during the first 14 days.

If the saturation targets are really resulting in a difference in bedside practice, they should have an impact on the oxygen exposure that the two groups receive.
The group assigned to the lower saturation target should be in lower FiO2.

Analysis: use the 3 FiO2 points/day to generate mean oxygen exposure each day (1st 14 days).
Examples:
Room air for 24 hours would be 0.21 x 24 = 5.04 O2-hrs
100% oxygen for 24 hrs would be 1.00x24 = 24.00 O2-hr
30% at time 1, 50% at time 2 and 29% at time 3 (let's assume times were 7, 9 and 8 hrs apart for the example).
0.30x7 + 0.50x9 + 0.29x8 = 2.10 + 4.50 + 2.32 = 8.92 O2-hrs

Then average O2-hrs for day 1 across group 1 vs group 2
Repeat for days 2,3,4...through 14

Plot: O2-hrs vs day after birth in groups 1 and 2

If the targets are resulting in different PRACTICE, the curves should reveal different oxygen exposure.

It would be supportive, indirect evidence (and maybe seen only by DSMC?). If there is no difference, we have a problem.

Codicle: if the ventilatory arm of the 2x2 design also affects the FiO2 received, it may have to be examined in four groups instead of two.

Dale
for Rochester

Percent of time spent at each SpO2 value (data processed as of 12/02/2005)

Data included in tables and graphs (includes days on supplemental oxygen only)

Data included	High target (91-95)	Low target (85-89)	Total
Infants	78	88	166
Hours	55849	46824	102673

Percent of time spent at each actual SpO2 value, by treatment group

	High target (91-95)		Low target (85-89)	
SpO2	Percent	Cumulative	Percent	Cumulative
<70	1.12	1.12	2.06	2.06
70	0.14	1.26	0.25	2.31
71	0.17	1.43	0.29	2.60
72	0.19	1.62	0.34	2.94
73	0.22	1.84	0.39	3.33
74	0.26	2.10	0.45	3.77
75	0.30	2.40	0.52	4.29
76	0.36	2.76	0.60	4.89
77	0.43	3.19	0.71	5.60
78	0.51	3.70	0.84	6.44
79	0.61	4.31	1.01	7.45
80	0.73	5.05	1.20	8.65
81	0.89	5.93	1.45	10.11
82	1.07	7.01	1.77	11.88
83	1.30	8.30	2.17	14.05
84	0.00	8.30	1.87	15.92
84.25	0.00	8.30	0.76	16.68
84.5	0.00	8.30	0.81	17.49
84.75	0.00	8.30	0.87	18.36
85	0.00	8.30	2.11	20.47
85.5	7.60	15.90	0.00	20.47
86	0.00	15.90	3.94	24.41
87	0.00	15.90	3.72	28.13
88	2.19	18.10	3.33	31.47
89	2.48	20.57	3.47	34.93
90	3.43	24.00	4.57	39.51
91	5.52	29.52	6.75	46.25
92	7.32	36.84	7.59	53.84
93	8.93	45.77	0.00	53.84
94	10.24	56.00	0.00	53.84
94.5	0.00	56.00	30.69	84.53
95	7.23	63.23	0.00	84.53
95.25	2.92	66.16	0.00	84.53
95.5	2.87	69.03	0.00	84.53
95.75	2.85	71.88	0.00	84.53
96	6.68	78.56	0.00	84.53
97	8.42	86.98	6.14	90.67
98	6.25	93.22	4.51	95.18
99	3.90	97.13	2.75	97.93
100	2.88	100.00	2.07	100.00

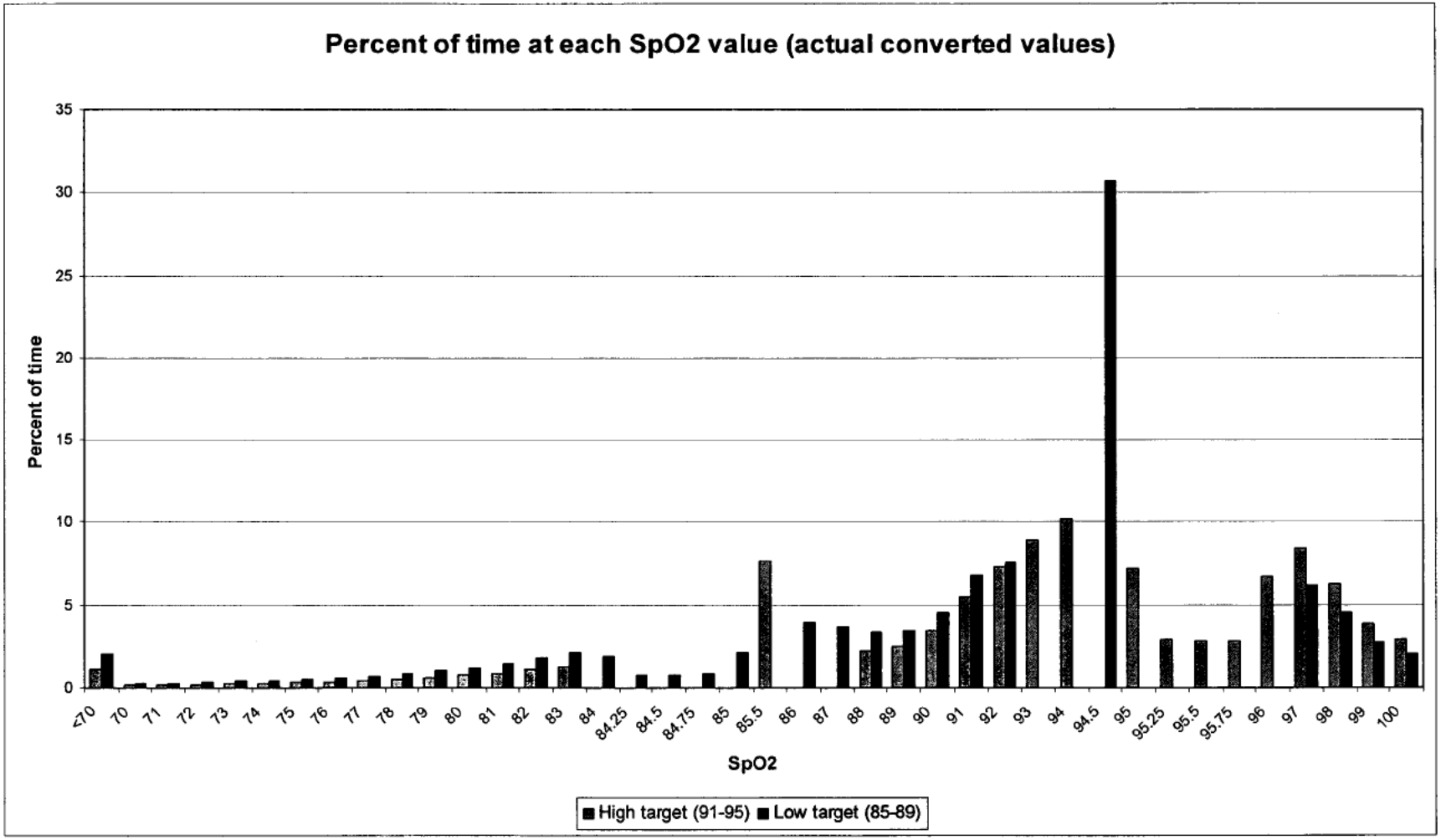
Median SpO2

	High target (91-95)	Low target (85-89)
Median	94	92

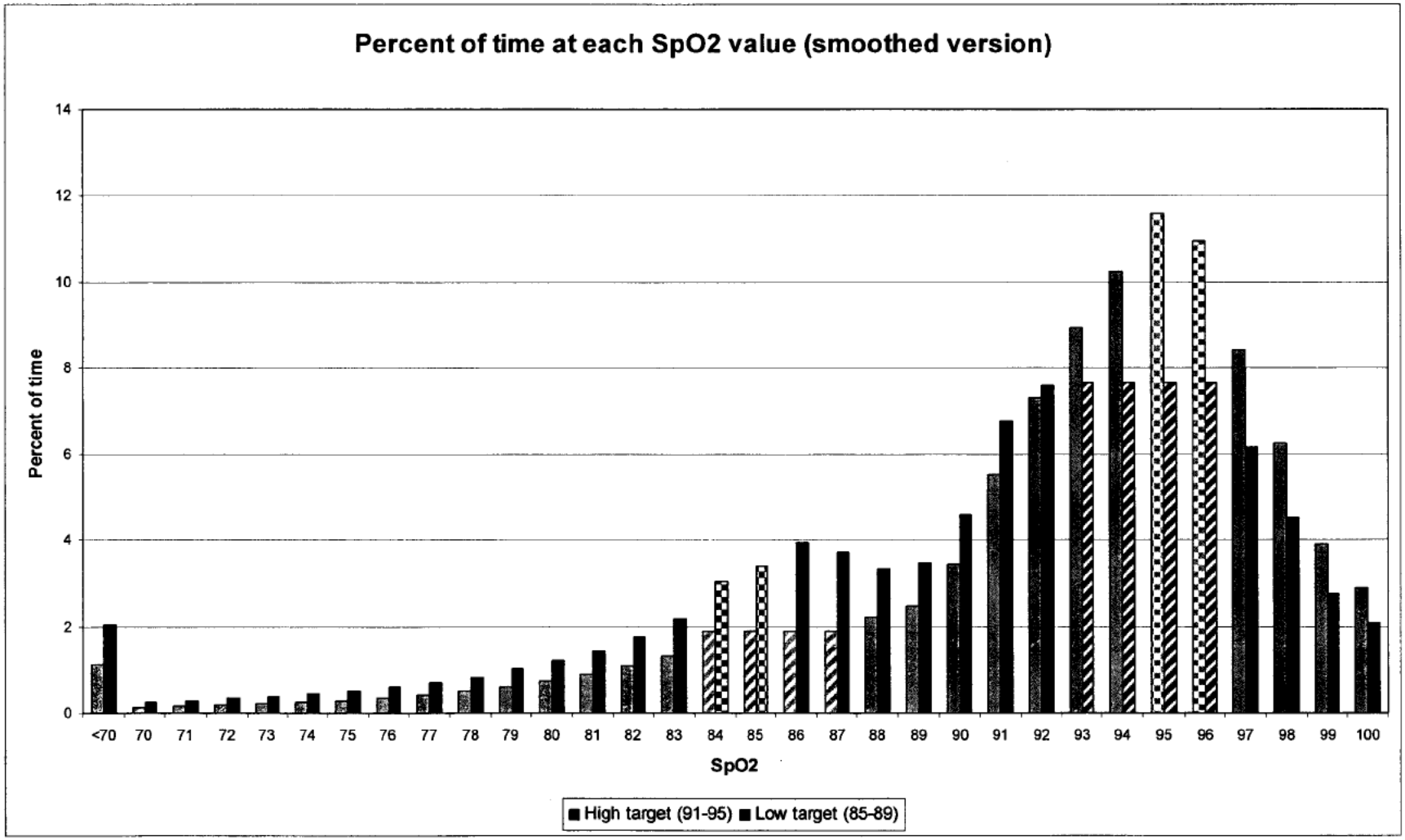
Percent of time of spent at SpO2 <84 and >96

Range	High target (91-95)	Low target (85-89)
<84	8.30	14.05
>96	21.44	15.47

The graph below displays each individual converted SpO2 value



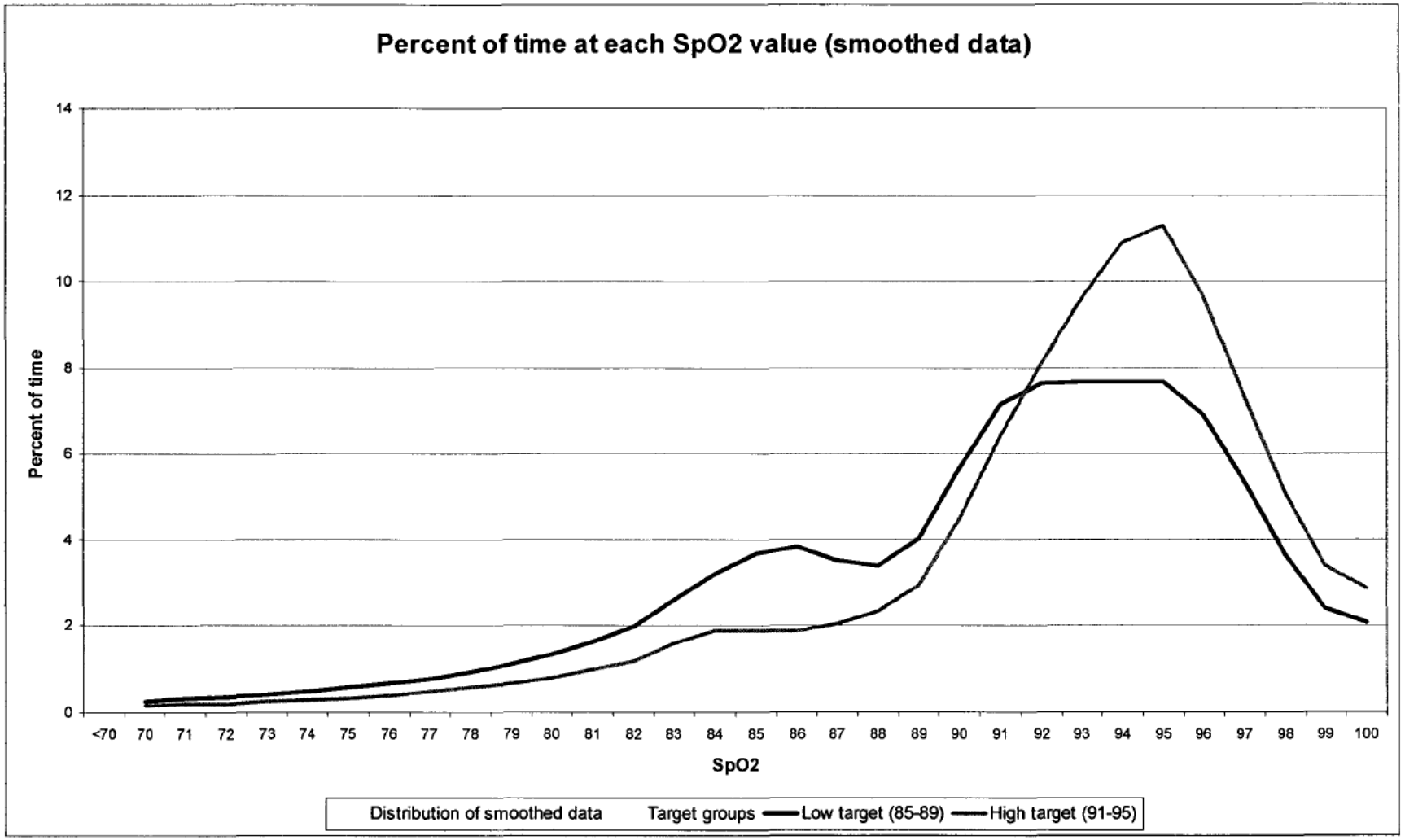
In the graph below, the converted SpO2 values have been smoothed to give a better idea of the distribution. Adjustments made to smooth the data are listed on the following page. Patterns are used to identify altered values.



Changes made to achieve smoothing

High target (91-95)	Pattern
Percent of time at converted value of 85.5 are spread evenly over 84-87	Blue diagonal stripes
Percent of time at 95 includes converted values of 95, 95.25 and half the percent of time at 95.5	Blue checked
Percent of time at 96 includes converted values of 96, 95.75 and half the percent of time at 95.5	Blue checked

Low target (85-89)	Pattern
Percent of time at converted value of 94.5 are spread evenly over 93-96	Burgundy diagonal stripes
Percent of time at 84 includes converted values of 84, 84.25 and half the percent of time at 84.5	Burgundy checked
Percent of time at 85 includes converted values of 85, 84.75 and half the percent of time at 84.5	Burgundy checked



From: Wally Carlo, M.D.
To: nfiner@ucsd.edu; AAF2@po.cwru.edu; bkh@rti.org; Edward.Donovan@chmcc.org; Higgins, Rosemary (NIH/NICHD) [E]; poo@rti.org; maynard.rasmussen@sharp.com; mcw3@po.CWRU.edu; sduara@miami.edu; wrich@ucsd.edu; Wally Carlo, M.D.
Subject: Re: DSMC SUPPORT Conference Call
Date: Saturday, December 03, 2005 1:18:54 PM

Neil and all. I agree with Neil's idea to lower the sat low alarm limit to 83% in those hospitals that want to establish that policy but it would probably be better for it to be a hospital polivy rather than a trial driven effort.
Wally
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: 'Avroy A. Fanaroff, M.D.' <aaf2@po.cwru.edu>; 'Betty Hastings' <bkh@rti.org>; 'Ed Donovan' <Edward.Donovan@chmcc.org>; higginsr@mail.nih.gov <higginsr@mail.nih.gov>; 'Ken Poole' <poo@rti.org>; Maynard Rasmussen <maynard.rasmussen@sharp.com>; 'Michele' <mcw3@po.cwru.edu>; 'Neil Finer' <nfiner@ucsd.edu>; 'Shahnaz Duara' <sduara@miami.edu>; 'Wade Rich' <wrich@ucsd.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Sat Dec 03 12:09:51 2005
Subject: FW: DSMC SUPPORT Conference Call

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Saturday, December 03, 2005 10:01 AM
To: 'Higgins, Rosemary (NIH/NICHD)'
Cc: 'Maynard.Rasmussen@sharp.com'; 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
Subject: RE: DSMC SUPPORT Conference Call

Good Day Rose

We discussed whether we should lower the limit to 80% and I understood that the response was to leave our alarms at the present level. I think that we should probably change the lower end to be in keeping with true SpO2 values - ie 83%. I would not increase the hi side as we only have 4 SpO2 points to play with, and we do not want the infants at 100% - we are currently at 99% and 100% for about 6.8% of the time in the 91-95 group, versus 4.8 in the 85 -89 group. I would suggest that we move the low alarm to 83# as this is the only value that is true for all oximeters. We will probably increase the time < 85% but if we increase the spread even further, that would be great. In addition we should think about the fact that our SpO2 medians differ by 2%. I think that this is evidence of the difference in SpO2 exposure between the groups -

High target (91-95)

Low target (85-89)

Median

94

92

The question is - what difference can we expect to achieve?

Our algorithm is only active maximally between 87% and 93%, and the fact that we return to normal works against us achieving a large spread. However, we are creating a difference in the entire SpO2 range.

I am of the belief that we will only be able to get to a 3% difference between the medians. More importantly how much difference to we want at the low and high ends - we currently have about 6% greater time below 84 in the 85-89 group, and about 7% less time > 97% for this group. Thus the low group is spending more time with lower actual sats

Range

High target (91-95)

Low target (85-89)

<84

8.30

14.05

>96

21.44

15.47

In a given 24 hour period, this group will therefore have (24X.07)=1.7 more hours each day with a SpO2 < 84%. Similarly the 91-95 group will have about the same duration with SpO2 values > 97% each day. I do not have any data which would indicate what differences we should aim for , and I am certain that with the numbers of data points that we have that these differences at the edges will be very significant (I would guess p<.00001). What difference is necessary to produce differential clinical outcomes? Do we already have enough difference?

As we further tighten up the time in the narrow range, I would anticipate that we will also increase these differences. Is there a difference or time time/day that we would consider too much at either end?

I would suggest that we have no such data, and that this study will determine these values.

However, I am anticipating the question of how much difference would be desirable? I would currently suggest that a target of 3% difference in the means may be a reasonable target, but I do not want to be held to that. We may discover that we already have enough difference when all the data are in for the study.

I would appreciate everyones' thoughts on these points as we prepare for the DSMC meeting.

Thanks for considering these issues.

Be well

Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 02, 2005 4:47 PM
To: nfiner@ucsd.edu
Subject: Re: DSMC SUPPORT Conference Call

Neil

Are we going to bring up a low saturation alarm limit of 80?? I am fine with what is written, but this had been discussed to avoid overshoot when oxygen gets turned up.

Thanks for all the hard work and effort.

Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----

From: Neil Finer <nfiner@ucsd.edu>

To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>

CC: Maynard.Rasmussen@sharp.com <Maynard.Rasmussen@sharp.com>; 'Avroy A. Fanaroff, M.D.' <aaf2@po.cwru.edu>; 'Betty Hastings' <bkh@rti.org>; 'Ed Donovan' <Edward.Donovan@chmcc.org>; 'Ken Poole' <poo@rti.org>; 'Michele' <mcw3@po.cwru.edu>; 'Neil Finer' <nfiner@ucsd.edu>; 'Shahnaz Duara' <sduara@miami.edu>; 'Wade Rich' <wrich@ucsd.edu>; 'Wally Carlo' <wcarlo@peds.uab.edu>

Sent: Fri Dec 02 12:39:48 2005

Subject: RE: DSMC SUPPORT Conference Call

Hi Rose

Here is the reworked reply and letter with everyone's suggestions included. I have attached all the relevant files. You may want to send them Marie's last hourly analyses which we quote. Your call as to whether they would appreciate this or not.

Thanks for your help

Are you swimming yet??

Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]

Sent: Friday, December 02, 2005 6:07 AM

To: Neil Finer

Subject: FW: DSMC SUPPORT Conference Call

Neil

Anything else to include in the email to the DSMC??

Thanks

Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]

Sent: Friday, December 02, 2005 9:06 AM

To: Higgins, Rosemary (NIH/NICHD)

Cc: Das, Abhik

Subject: RE: DSMC SUPPORT Conference Call

Yes, I believe Neil sent them. I'll plan to send them the following:

Agenda and list of participants

List of members with their specialty, etc.

SUPPORT Protocol

Letter of Response from the Steering Committee

The two abstracts.

Anything else?

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]

Sent: Friday, December 02, 2005 9:00 AM

To: Hastings, Betty J.

Subject: RE: DSMC SUPPORT Conference Call

The PI's had until last night to weight in – Neil will do it today.

Can we also send the Hagadorn abstract and the Case Western Abstract to them? Do you have the files for both?

Thanks

Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]

Sent: Friday, December 02, 2005 8:58 AM

To: Higgins, Rosemary (NIH/NICHD)

Subject: RE: DSMC SUPPORT Conference Call

Do you know when the letter will be ready to send out to the DSMC?

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD) [E]
Cc:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Subject:	FW: New data
Date:	Friday, December 02, 2005 8:13:06 PM
Attachments:	Percent of time spent at each SpO2 value 12-2-05.doc Response to DSMC Steering Final1.doc

Hi Rose
The most recent data the differences between the groups persist, but is somewhat less with more numbers as suspected. This is a better representation of the study to date. – I have added these to the latest DMC response attached.
Rose, please use this version. We probably would want to send this file to the DSMC (Percent of time 12-2-05)
As always, your call
Be well
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, December 02, 2005 2:13 PM
To: nfiner@ucsd.edu
Cc: Das, Abhik; Poole, W. Kenneth
Subject: New data

Hi Neil,

Attached is another pulse ox data update. This one is based on 166 out of a total of 173 infants, so it should be very representative of what our data look like as a whole. I will send you a revision based on all of the infants on Monday.

Notice that, in addition to the graph showing the percent of time spent at each converted (actual) SpO2 value, there are two additional graphs. One is a bar graph in which the numbers have been redistributed to achieve a smoothed effect. There is a table in the document explaining how the smoothing was done. The third and final graph shows the distribution for each treatment group which has been smoothed a little bit more.

Have a good weekend.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone (919) 485-7780
Fax (919) 485-7762
mgantz@rti.org

Percent of time spent at each SpO2 value (data processed as of 12/02/2005)

Data included in tables and graphs (includes days on supplemental oxygen only)

Data included	High target (91-95)	Low target (85-89)	Total
Infants	78	88	166
Hours	55849	46824	102673

Percent of time spent at each actual SpO2 value, by treatment group

	High target (91-95)		Low target (85-89)	
SpO2	Percent	Cumulative	Percent	Cumulative
<70	1.12	1.12	2.06	2.06
70	0.14	1.26	0.25	2.31
71	0.17	1.43	0.29	2.60
72	0.19	1.62	0.34	2.94
73	0.22	1.84	0.39	3.33
74	0.26	2.10	0.45	3.77
75	0.30	2.40	0.52	4.29
76	0.36	2.76	0.60	4.89
77	0.43	3.19	0.71	5.60
78	0.51	3.70	0.84	6.44
79	0.61	4.31	1.01	7.45
80	0.73	5.05	1.20	8.65
81	0.89	5.93	1.45	10.11
82	1.07	7.01	1.77	11.88
83	1.30	8.30	2.17	14.05
84	0.00	8.30	1.87	15.92
84.25	0.00	8.30	0.76	16.68
84.5	0.00	8.30	0.81	17.49
84.75	0.00	8.30	0.87	18.36
85	0.00	8.30	2.11	20.47
85.5	7.60	15.90	0.00	20.47
86	0.00	15.90	3.94	24.41
87	0.00	15.90	3.72	28.13
88	2.19	18.10	3.33	31.47
89	2.48	20.57	3.47	34.93
90	3.43	24.00	4.57	39.51
91	5.52	29.52	6.75	46.25
92	7.32	36.84	7.59	53.84
93	8.93	45.77	0.00	53.84
94	10.24	56.00	0.00	53.84
94.5	0.00	56.00	30.69	84.53
95	7.23	63.23	0.00	84.53
95.25	2.92	66.16	0.00	84.53
95.5	2.87	69.03	0.00	84.53
95.75	2.85	71.88	0.00	84.53
96	6.68	78.56	0.00	84.53
97	8.42	86.98	6.14	90.67
98	6.25	93.22	4.51	95.18
99	3.90	97.13	2.75	97.93
100	2.88	100.00	2.07	100.00

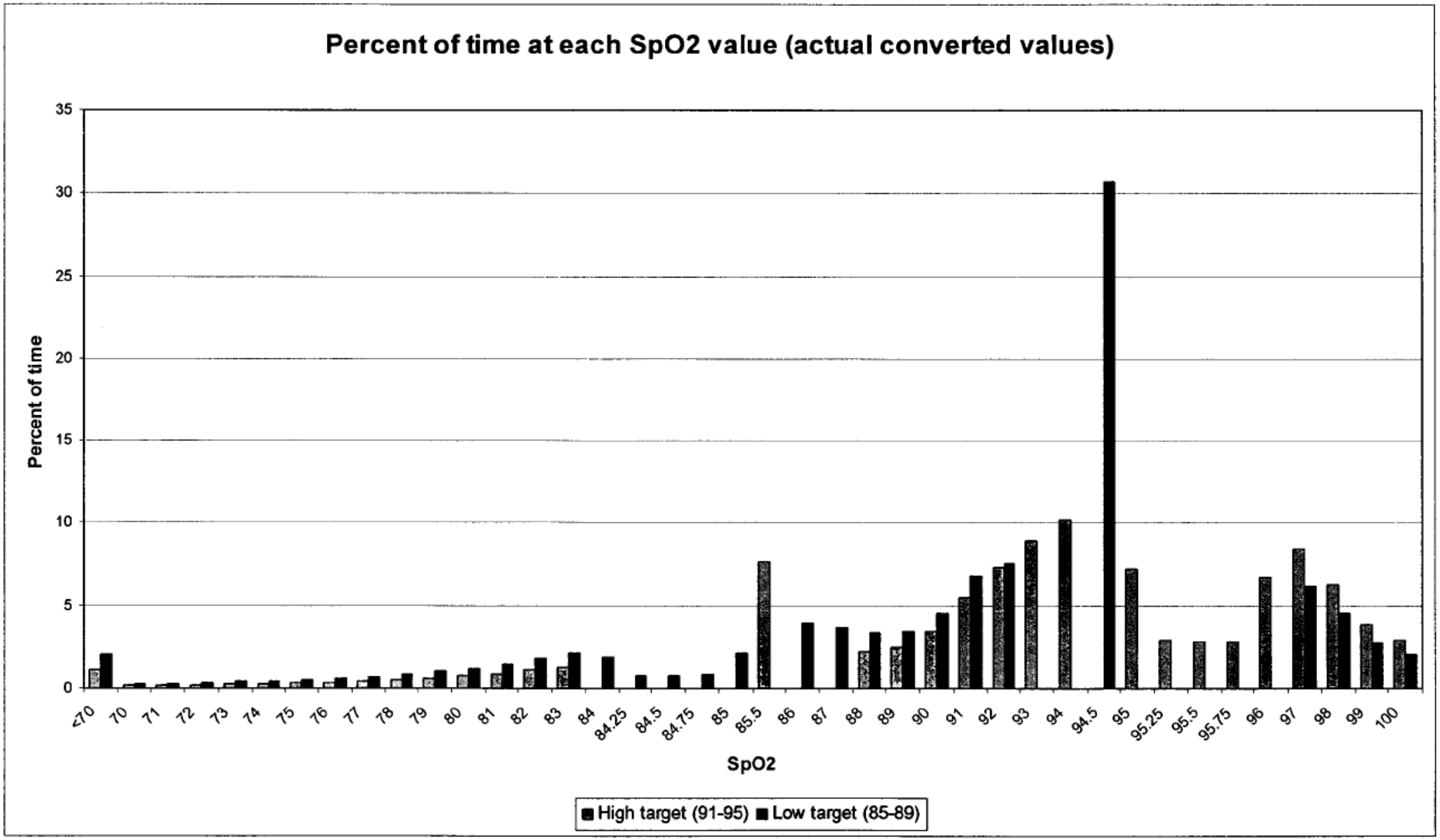
Median SpO2

	High target (91-95)	Low target (85-89)
Median	94	92

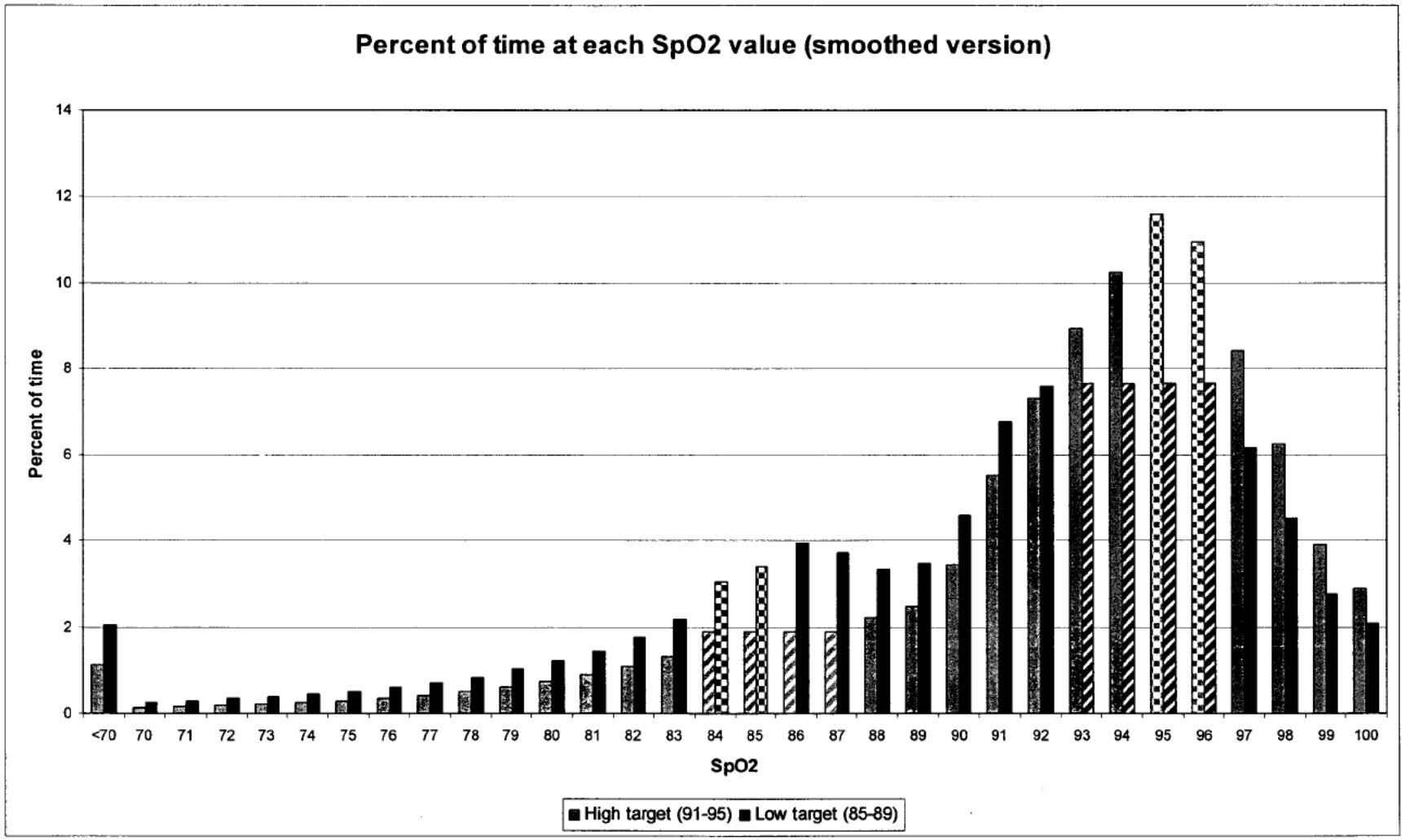
Percent of time of spent at SpO2 <84 and >96

Range	High target (91-95)	Low target (85-89)
<84	8.30	14.05
>96	21.44	15.47

The graph below displays each individual converted SpO2 value



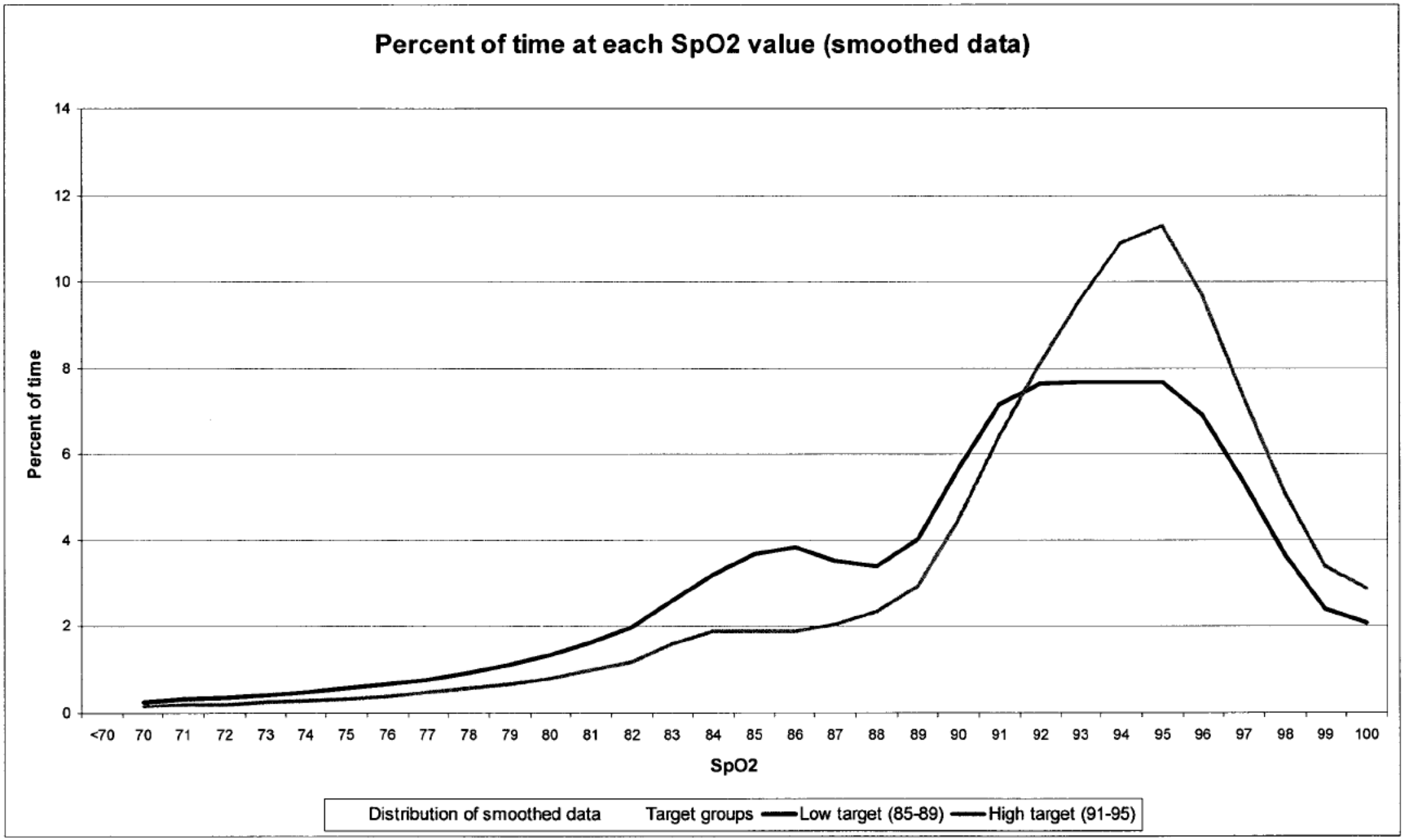
In the graph below, the converted SpO2 values have been smoothed to give a better idea of the distribution. Adjustments made to smooth the data are listed on the following page. Patterns are used to identify altered values.



Changes made to achieve smoothing

High target (91-95)	Pattern
Percent of time at converted value of 85.5 are spread evenly over 84-87	Blue diagonal stripes
Percent of time at 95 includes converted values of 95, 95.25 and half the percent of time at 95.5	Blue checked
Percent of time at 96 includes converted values of 96, 95.75 and half the percent of time at 95.5	Blue checked

Low target (85-89)	Pattern
Percent of time at converted value of 94.5 are spread evenly over 93-96	Burgundy diagonal stripes
Percent of time at 84 includes converted values of 84, 84.25 and half the percent of time at 84.5	Burgundy checked
Percent of time at 85 includes converted values of 85, 84.75 and half the percent of time at 84.5	Burgundy checked



In response to the comments and concerns of the DSMC, the SUPPORT committee held a conference call Monday Nov 28th at 10:00 to 1130AM to prepare a response. This issue and the preparation of a response was then discussed by the entire NICHD Neonatal Research Network Steering Committee in a conference call held Wednesday. Nov 30th at 9:30 – 11:00 AM. This response has been reviewed by the SUPPORT Subcommittee, and subsequently by the Steering Committee, and reflects the input of all NICHD Principal Investigators.

- The DSMC made the following 2 comments in their letter regarding the SUPPORT trial. This was generated after they reviewed the oximeter data, which was corrected back to actual SpO2 values from the altered values displayed at the bedside:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

We have responded to each of these concerns and our responses are detailed below

Response to Issue Number 1

We appreciate the concern expressed by the DSMC regarding a potential safety issue secondary to durations of SpO2 values greater than 95%.

1. Review of existing evidence and practice regarding durations of higher SpO2 values:

To date there are no prospective data which define the SpO2s experienced by the ELBW infant from birth as part of usual clinical care. Because no published studies have evaluated the effects of different target SpO2 ranges from birth on important outcomes, this was one of the principle reasons for the design and conduct of the SUPPORT trial.

A number of studies have evaluated different alarm limits, but have not reported the actual durations of SpO2 in the various ranges. Nghiem et al in a PAS abstract this year reported that nurses caring for ELBW infants believe that an acceptable oxygen saturation range should include higher upper limits than

specified by current policy (Nghiem et al, Nursing Opinions and Practices of Oxygenation in Prematures: The NOPOP Study PAS #3415, 2005). The study by Hagadorn reported as a late breaker at the PAS last year (Hagadorn et al, Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation. PAS 2004, Attached) did report on the experience of monitoring the actual SpO2 for 72 hours in the first 4 weeks of life in 78 ELBW infants. They reported that the "lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for a median of 70 hours (25th-75th percentiles 67-71 hr) during each of the first 24 weeks. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25th-75th percentiles 91-97%; range of study center medians 91-96%. Centers ranged between 16-71% compliance with their individual intended SpO2 range. Most noncompliance was above intended range." In comparing the SUPPORT data evaluated to date by the DSMC, it is of interest that the mean SpO2 in the 2 Oximeter arms is 90% and 92%, with medians of 92% and 94%, all of which are below that reported by Hagadorn et al (median=95).

The 2 other relevant trials, STOP-ROP and BOOST, both enrolled infants of > 32 weeks postmenstrual age (PMA), and maintained 2 levels of SpO2, 89% to 94% and 91-94% versus 95% to 98% and 96% to 99%, by administration of oxygen. These studies achieved reasonable separation, but did demonstrate substantial overlap of the intended ranges (estimated to be 50% or greater, D Phelps, PI for STOP-ROP). It is important to note that these studies were testing two ranges both of which were higher than the lower range of the SUPPORT trial (85% to 89%) and were treating infants who, for the most part, had recovered from their acute disease. In the BOOST trial 70% of the enrolled infants were < 28 weeks of age at birth (all of SUPPORT is < 28 weeks), 32 weeks PMA, and required oxygen at enrollment (Askie et al, New England Journal of Medicine. 2003; 349(10):959-967). The STOP-ROP trial enrolled infants with pre-threshold ROP at a PMA of 35.4 + 2.5 weeks of age (Phelps et al, Pediatrics. 2000; 105(2):295-310). These trials then gave the higher SpO2 range infants additional oxygen to increase their SpO2 to the desired range. STOP-ROP reported that the infants in the high range had an SpO2 > 95% for > 97% of the monitored time. These studies found an overall increase in pulmonary morbidity in the higher SpO2 range infants.

Examination of oximeter data from one of the NRN sites (Case Western, Walsh et al) obtained for an ongoing study evaluating infants similar to those enrolled in SUPPORT, and managed with conventional oximeters, revealed that for the 9 infants for whom results were available that the percentage of time with and SpO2 > 95% was > 50%.

2. Impact of SUPPORT oximeters algorithm on sat values:

The oximetry algorithm that was designed for the SUPPORT trial is such that re-conversion of the altered oximeter values does not result in a discrete SpO2 number for every displayed value. SpO2 values, of 93%, 94% 95% and 96% will all be reconverted to a single value. As an example, when the actual percent of time at each individual SpO2 point was calculated for this review, in

the 91% to 95% group, there was 5.76% of the time spent at an actual SpO2 of 96% and 8.38% of the time spent at values that represented conversion from readings of 93% to 95%. In the 85% to 89% arm, values of 84%, 85%, 86% and 87% will be reconverted to a single value of 84%. This is a result of having the displayed values return to non-skewed SpO2 values at < 84% and > 96%, a safety design felt to be important by all involved in this trial (See Attached file USCD1). Thus the percentages reported to the DSMC for some of the ranges that include these values were not an accurate representation of the true values. However all values > 96% and < 84% are actual and do not require any conversion.

Percent of time of spent at SpO2 < 84% and > 96%
(RTI, Dec 2, 2005)

Range **Assigned**	High target (91-95)	Low target (85-89)
< 84%	8.30	14.05
> 96%	21.45	15.47

In the current SUPPORT study, an initial analyses utilizing only unaltered SpO2 values as shown above , ie those below 84% and above 96%, have shown that one arm had an SpO2 > 96% for 15.47% versus 21.45% of the time for the comparison arm, and the duration of an SpO2 < 84% was also different at 14.05% versus 8.30%. The values for SpO2s > 96% using unaltered data suggests that the SUPPORT trial to date has, if anything, reduced the duration of higher oxygen saturations.

In addition, analyses using only actual SpO2 demonstrate that the infants in this trial who are receiving supplemental oxygen are spending approximately 70% of the time with a true SpO2 value between 84% and 96%. We believe that this is information is very encouraging.

3. Impact of inclusion of data from periods in room air on saturation distributions:

As part of the SUPPORT trial, we collect information about inhaled oxygen concentration 3 times a day for the first 14 days and daily thereafter. We believe that an improved documentation of the times when infants are on room air will allow us to determine the saturations during actual oxygen exposure. At the present an infant is considered to be receiving supplemental oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized as receiving supplemental oxygen for significant periods when they are actually in room air. This would result in durations of SpO2 greater than 95% that were felt to be modifiable and reported as such when in fact there is no effective treatment for such elevated SpO2s. In addition, we do not know if such SpO2s on room air are associated with any morbidity. From the SUPPORT study data analyses to date we know that infants in room air have SpO2s > 95% for 46% to 69% of the time.

In view of this design, we would suggest that all future interval analyses for safety examine the ranges of <84% and >96% as those ranges that are considered to be low and high.

We believe that the SUPPORT trial will actually define the periods of time that ELBW infants spend with different ranges of SpO2, and that it is essential to collect this information. In addition, as our findings indicate a lower true percent of the time at SpO2 values >95%, and lower median SpO2 values than has previously been reported, we are in fact, reducing the time with high SpO2 values compared to usual care. The SUPPORT trial carefully evaluates risks, and we will be evaluating group differences for all important short and long term outcomes.

The SUPPORT trial methodology actively encourages all caretakers to keep SpO2 < 96% by having alarm limits set at 85% and 95%. These limits were utilized because it was felt that these represented current practice. The oximetry algorithms were designed to keep infants in the narrower target range of 88% to 92% with the realization that setting alarm limits at these values would severely increase the frequency of the alarms sounding. Nevertheless, our results to date suggest that we have decreased the expected percent of time > 95%, and in one group the value of 14% may be as low as is achievable in an actual clinical environment given the evidence provided by Hagadorn et al and Nghiem et al.

We believe the SUPPORT study will define the distribution and durations of pulse oximetry values among premature infants in highly staffed, dedicated academic centers, and among infants randomized to two different target ranges. For this reason alone, the SUPPORT trial will be very valuable. All of the procedures outlined below in response to your second concern will also allow us to further increase the percentage of time that the infants are in the maximally altered SpO2 ranges which we believe will further increase separation of these groups.

Response to Issue Number 2

There is concern that we have not achieved adequate separation by the current oximeters and study personnel.

1. As described above, the results of additional analyses performed in response to the concerns of the DSMC show differences in the durations of low and high SpO2s between the 2 oximeter groups. A careful analysis of the most recent converted values demonstrates that the cumulative time spent with an SpO2 of 90% or less is 24.0% (91% - 95%) versus 39.5% (85% - 89%), for the 2 oximeter groups, supporting the ability of the altered oximeters to produce differential SpO2 exposures.

2. We do acknowledge that it would be desirable to increase the percentage of time in the narrower target range and towards this end would propose the following changes to SUPPORT:

A. We will require **documentation that the alarm limits are set and functional as per protocol every 4-6 hours**. We have found that in some units the high alarms are being turned off, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned to the most appropriate personnel in each unit, which may include bedside or research nurses or respiratory therapists, and this procedure is already being done in many NRN units.

B. We will immediately initiate a **change in our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect saturations measured while on oxygen therapy and exclude saturations of infants in room air.** We will change the data form to indicate that the infant was either in oxygen for the entire 24 hours, and if not, will provide a more accurate estimate of the true time in oxygen, and we will continue with this form of data collection for the entire time that the infant is receiving oxygen. In the current protocol we collect such information 3 times a day for the first 14 days only and then daily thereafter. We believe that more frequent and extended documentation will allow us to determine more accurately the actual time that an infant is in room air. At the present the infant is considered to have spent a day in oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized in oxygen for significant periods when they are in room air. While in room air, we cannot manipulate the SpO2, and thus knowledge of the true time in oxygen will produce a more accurate representation of oximetry results that are subject to care interventions.

C. We will initiate **further training and in-service at all the sites to stress the importance of keeping the SpO2 alarms functional and at the limits of 85% and 95%**. In the past these were guidelines, and we will now change the study manual and protocol to indicate these limits are now set by protocol and that violations will be documented. We will encourage all caretakers to aim for an SpO2 value of 90% and make every effort to educate caretakers to make smaller adjustments in FiO2 and ensure that the infant is maintained between the 87% to 93%, the range with the maximal separation of the study oximeters. We will further facilitate the use of the 2 hour and 12 hour histograms showing the infants' actual ranges to provide feedback to the caretakers regarding the percentage of time in the target ranges.

D. We will develop **guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation**. More modulated increases in oxygen during these desaturation events will minimize overshoot and the potential of high SpO2 values. We would hope that such changes – ie increasing the FiO2 in steps of 5% as opposed to much larger increases will decrease the resultant overshoots creating the high SpO2 values. This will be included in the revised manual of operations.

E. **We will place bedside cards to indicate the target range**.

F. We will **initiate compliance monitoring visits coordinated by RTI to visit random sites**. These visits had been planned, but had not yet been initiated. The teams will consist of a member of RTI and a study coordinator, and they will review the adherence to the protocol and any other relevant issues.

G. We would recommend that at a minimum, the unblinded oximetry data be reviewed again after an additional 100 to 150 infants have been enrolled in this trial.

We thank the DSMC for their thoughtful concerns. We trust that our plans to move forward with the SUPPORT trial are acceptable to the DSMC. We are anxious to initiate the above changes, seek IRB approvals and re-activate this trial.

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: DSMC SUPPORT Conference Call
Date: Friday, December 02, 2005 4:07:48 PM

Thanks. I hope you have a safe trip and that (b) (6) (b) (6) .

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 02, 2005 4:06 PM
To: Hastings, Betty J.
Cc: nfiner@ucsd.edu
Subject: Re: DSMC SUPPORT Conference Call

I need to review this and then it can be sent. I will look at it tonight or tomorrow and and get back to both of you.

Thanks for all the help
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Hastings, Betty J. <bkh@rti.org>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
CC: nfiner@ucsd.edu <nfiner@ucsd.edu>
Sent: Fri Dec 02 16:04:52 2005
Subject: RE: DSMC SUPPORT Conference Call

Rose,
Are we ready to send these on Monday with the other material?

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Friday, December 02, 2005 12:40 PM
To: 'Higgins, Rosemary (NIH/NICHD)'
Cc: Maynard.Rasmussen@sharp.com; 'Avroy A. Fanaroff, M.D.'; Hastings, Betty J.; 'Ed Donovan'; Poole, W. Kenneth; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
Subject: RE: DSMC SUPPORT Conference Call

Hi Rose

Here is the reworked reply and letter with everyone's suggestions included. I have attached all the relevant files. You may want to send them Marie's last hourly analyses which we quote. Your call as to whether they would appreciate this or not.

Thanks for your help

Are you swimming yet??

Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 02, 2005 6:07 AM
To: Neil Finer
Subject: FW: DSMC SUPPORT Conference Call

Neil

Anything else to include in the email to the DSMC??
Thanks

Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Friday, December 02, 2005 9:06 AM
To: Higgins, Rosemary (NIH/NICHD)
Cc: Das, Abhik
Subject: RE: DSMC SUPPORT Conference Call

Yes, I believe Neil sent them. I'll plan to send them the following:

Agenda and list of participants

List of members with their specialty, etc.

SUPPORT Protocol

Letter of Response from the Steering Committee

The two abstracts.

Anything else?

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 02, 2005 9:00 AM
To: Hastings, Betty J.
Subject: RE: DSMC SUPPORT Conference Call

The PI's had until last night to weight in - Neil will do it today.

Can we also send the Hagadorn abstract and the Case Western Abstract to them? Do you have the files for both? Thanks

Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Friday, December 02, 2005 8:58 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: DSMC SUPPORT Conference Call

Do you know when the letter will be ready to send out to the DSMC?

From: Neil Finer
To: "Das, Abhik"; "Tyson, Jon E"; Higgins, Rosemary (NIH/NICHD) [E]; "Carlo Waldemar (E-mail)"; "Michelle Walsh"; "Morris, Brenda H"
Cc: wrich@ucsd.edu
Subject: RE:
Date: Friday, December 02, 2005 2:47:46 PM

Hi Jon
I agree with concerns that we do not collect excessive data. Our current thought is that we indicate whether a child was on oxygen for an entire day of not. If not, we then ask the coordinator to review that day and assign the infants to either room air or oxygen based on which mode was the more prevalent during the day – that will be better than current but not result in excessive data. We also agree that we need site visits, and will include this monitoring as one the of the purposes of that visit.
Thanks for your comments
Neil

From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, December 02, 2005 11:07 AM
To: Tyson, Jon E; Higgins, Rosemary (NIH/NICHD); Neil Finer; Carlo Waldemar (E-mail); Michelle Walsh; Morris, Brenda H
Subject: RE:

Jon:

In answer to your question for me, in our reported analyses we have only included days on which we know the infant received supplemental oxygen. Thus, if the SUPP05 and SUPP11 have not been submitted for the infant, he or she is not included.

Regarding your suggestion about FiO2 data collection, as Neil knows, I am all for limited data collection, and would support whatever reasonable approach that can achieve it! (Our data processing resources are stretched as is with the volume of pulse ox data that we are having to deal with!) But, I thought that the purpose of collecting more FiO2 data was to allow us to identify when the infants were on supplemental oxygen during the course of the day. If this is the case, then the random audit approach may not be very useful, though I definitely hear your point about the accuracy and credibility of any data we collect on this score.

Thanks

Abhik

> -----Original Message-----
> **From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]
> **Sent:** Friday, December 02, 2005 1:23 PM
> **To:** Das, Abhik; Higgins, Rosemary (NIH/NICHD); Neil Finer; Carlo Waldemar (E-mail); Michelle Walsh; Morris, Brenda H
> **Subject:**
>
> Neil, I was out of town and unable to be on the conference call. It seems to me that the proposal is to spend an enormous amount of time to collect data that still may not be very interpretable. Even if we had saturation and FiO2 for every baby for every hour as taken off the nursing flow sheets, it would be a big stretch to believe that these were necessarily accurate or that FiO2 and oxygen saturation were recorded at the same time (or even with several minutes of each other). If there is to be greater scrutiny of the flow sheets and nursing compliance using the flow sheet, it may well be that nurses—like other people---would be less likely to values that would prompt criticism. It is quite plausible that they would instead wait to a later moment to record data at a time when the values would be considered to be appropriate.

Would you consider instead a random audit in which the respiratory therapists (at any time) and/or research nurses (during the day) would at randomly selected times and babies (which could be selected by RTI), walk up to the bedside and record the FiO2 and saturation at that moment. With 16 centers, it wouldn't take very many observations to get a reasonably precise estimate of the proportion of time that the FiO2 was inappropriate. This could be done on a continuous basis or intermittently as desired and would require much less data recording, analytic effort, and total cost and be much more likely to be accurate and unbiased. It would also give information about inappropriately low FiO2.

Abhik

Georgia and I want to be sure that the saturation analyses were really limited to those infants for whom the clinical data had been submitted that would allow the analyst to have some chance to relate the saturation data to whether the infants were receiving oxygen for part of the day. In our site, oximeter download had been submitted for approximately 14 infants before 11/7. However, supp 05 and supp 11 (both needed to assess FiO2 at the ages when the oximeter downloads were obtained) had been submitted for only 7 infants) Can you sort your data quickly and determine whether there were others infants included in the analysis of oxygen saturation? If so, then there may be other babies who were inadvertently included in the analysis from other centers.

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

From: Spong, Catherine (NIH/NICHD)
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT Trial
Date: Friday, December 02, 2005 1:10:56 PM

AMEN

Catherine Y Spong MD
Chief, Pregnancy and Perinatology Branch, NICHD, NIH
6100 Executive Blvd, Rm 4B03, MSC 7510
Bethesda MD 20892 (express mail: Rockville MD 20852)
Phone 301 435 6894 or 301 496 5575
Fax 301 496 3790
email spongc@mail.nih.gov

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD)
Sent: Friday, December 02, 2005 1:08 PM
To: Hanson, James (NIH/NICHD); Spong, Catherine (NIH/NICHD)
Subject: Fw: SUPPORT Trial

FYI
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Alexander, Duane (NIH/NICHD) <alexandd@exchange.nih.gov>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
CC: Hanson, James (NIH/NICHD) <hansonj@mail.nih.gov>
Sent: Fri Dec 02 13:01:23 2005
Subject: RE: SUPPORT Trial

Hi Rose - No need to do anything with the Registry if the down-time will probably be this short.
Duane

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD)
Sent: Monday, November 28, 2005 4:58 PM
To: Alexander, Duane (NIH/NICHD)
Cc: Hanson, James (NIH/NICHD); Spong, Catherine (NIH/NICHD)
Subject: Re: SUPPORT Trial

Hi,
(b) (5) [redacted]

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Alexander, Duane (NIH/NICHD) <alexandd@exchange.nih.gov>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Mon Nov 28 16:48:14 2005
Subject: RE: SUPPORT Trial

Hi Rose –

I agree with (b) (5) [redacted]

Duane

From: Higgins, Rosemary (NIH/NICHD)
Sent: Wednesday, November 23, 2005 10:14 AM
To: Alexander, Duane (NIH/NICHD)
Cc: Spong, Catherine (NIH/NICHD); Hanson, James (NIH/NICHD)
Subject: SUPPORT Trial

Hi Duane,

I spoke to Jim Hanson regarding the SUPPORT trial enrollment suspension this AM. He suggested that (b) (6) [redacted]

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD) [E]
Cc:	Maynard.Rasmussen@sharp.com; "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Subject:	RE: DSMC SUPPORT Conference Call
Date:	Friday, December 02, 2005 12:40:12 PM
Attachments:	Response to DSMC Steering Final.doc 20040226AVIOxLateBreakerDraft.doc ucsd1.doc Avery Letter.doc Percent of time spent at each SpO2 value.doc

Hi Rose
Here is the reworked reply and letter with everyone's suggestions included. I have attached all the relevant files. You may want to send them Marie's last hourly analyses which we quote. Your call as to whether they would appreciate this or not.
Thanks for your help
Are you swimming yet??
Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 02, 2005 6:07 AM
To: Neil Finer
Subject: FW: DSMC SUPPORT Conference Call

Neil
Anything else to include in the email to the DSMC??
Thanks
Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Friday, December 02, 2005 9:06 AM
To: Higgins, Rosemary (NIH/NICHD)
Cc: Das, Abhik
Subject: RE: DSMC SUPPORT Conference Call

Yes, I believe Neil sent them. I'll plan to send them the following:
Agenda and list of participants
List of members with their specialty, etc.
SUPPORT Protocol
Letter of Response from the Steering Committee
The two abstracts.

Anything else?

> -----Original Message-----
> **From:** Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> **Sent:** Friday, December 02, 2005 9:00 AM
> **To:** Hastings, Betty J.
> **Subject:** RE: DSMC SUPPORT Conference Call
>
> The PI's had until last night to weight in – Neil will do it today.
>
> Can we also send the Hagadorn abstract and the Case Western Abstract to them? Do you have the files for both?
> Thanks

Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Friday, December 02, 2005 8:58 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: DSMC SUPPORT Conference Call

Do you know when the letter will be ready to send out to the DSMC?

In response to the comments and concerns of the DSMC, the SUPPORT committee held a conference call Monday Nov 28th at 10:00 to 1130AM to prepare a response. This issue and the preparation of a response was then discussed by the entire NICHD Neonatal Research Network Steering Committee in a conference call held Wednesday. Nov 30th at 9:30 – 11:00 AM. This response has been reviewed by the SUPPORT Subcommittee, and subsequently by the Steering Committee, and reflects the input of all NICHD Principal Investigators.

- The DSMC made the following 2 comments in their letter regarding the SUPPORT trial. This was generated after they reviewed the oximeter data, which was corrected back to actual SpO2 values from the altered values displayed at the bedside:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

We have responded to each of these concerns and our responses are detailed below

Response to Issue Number 1

We appreciate the concern expressed by the DSMC regarding a potential safety issue secondary to durations of SpO2 values greater than 95%.

1. Review of existing evidence and practice regarding durations of higher SpO2 values:

To date there are no prospective data which define the SpO2s experienced by the ELBW infant from birth as part of usual clinical care. Because no published studies have evaluated the effects of different target SpO2 ranges from birth on important outcomes, this was one of the principle reasons for the design and conduct of the SUPPORT trial.

A number of studies have evaluated different alarm limits, but have not reported the actual durations of SpO2 in the various ranges. Nghiem et al in a PAS abstract this year reported that nurses caring for ELBW infants believe that an acceptable oxygen saturation range should include higher upper limits than

specified by current policy (Nghiem et al, Nursing Opinions and Practices of Oxygenation in Prematures: The NOPOP Study PAS #3415, 2005). The study by Hagadorn reported as a late breaker at the PAS last year (Hagadorn et al, Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation. PAS 2004, Attached) did report on the experience of monitoring the actual SpO2 for 72 hours in the first 4 weeks of life in 78 ELBW infants. They reported that the "lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for a median of 70 hours (25th-75th percentiles 67-71 hr) during each of the first 24 weeks. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25th-75th percentiles 91-97%; range of study center medians 91-96%. Centers ranged between 16-71% compliance with their individual intended SpO2 range. Most noncompliance was above intended range." In comparing the SUPPORT data evaluated to date by the DSMC, it is of interest that the mean SpO2 in the 2 Oximeter arms is 90% and 92%, with medians of 92% and 94%, all of which are below that reported by Hagadorn et al (median=95).

The 2 other relevant trials, STOP-ROP and BOOST, both enrolled infants of > 32 weeks postmenstrual age (PMA), and maintained 2 levels of SpO2, 89% to 94% and 91-94% versus 95% to 98% and 96% to 99%, by administration of oxygen. These studies achieved reasonable separation, but did demonstrate substantial overlap of the intended ranges (estimated to be 50% or greater, D Phelps, PI for STOP-ROP). It is important to note that these studies were testing two ranges both of which were higher than the lower range of the SUPPORT trial (85% to 89%) and were treating infants who, for the most part, had recovered from their acute disease. In the BOOST trial 70% of the enrolled infants were < 28 weeks of age at birth (all of SUPPORT is < 28 weeks), 32 weeks PMA, and required oxygen at enrollment (Askie et al, New England Journal of Medicine. 2003; 349(10):959-967). The STOP-ROP trial enrolled infants with pre-threshold ROP at a PMA of 35.4 + 2.5 weeks of age (Phelps et al, Pediatrics. 2000; 105(2):295-310). These trials then gave the higher SpO2 range infants additional oxygen to increase their SpO2 to the desired range. STOP-ROP reported that the infants in the high range had an SpO2 > 95% for > 97% of the monitored time. These studies found an overall increase in pulmonary morbidity in the higher SpO2 range infants.

Examination of oximeter data from one of the NRN sites (Case Western, Walsh et al) obtained for an ongoing study evaluating infants similar to those enrolled in SUPPORT, and managed with conventional oximeters, revealed that for the 9 infants for whom results were available that the percentage of time with and SpO2 > 95% was > 50%.

2. Impact of SUPPORT oximeters algorithm on sat values:

The oximetry algorithm that was designed for the SUPPORT trial is such that re-conversion of the altered oximeter values does not result in a discrete SpO2 number for every displayed value. SpO2 values, of 93%, 94% 95% and 96% will all be reconverted to a single value. As an example, when the actual percent of time at each individual SpO2 point was calculated for this review, in

the 91% to 95% group, there was 5.76% of the time spent at an actual SpO2 of 96% and 8.38% of the time spent at values that represented conversion from readings of 93% to 95%. In the 85% to 89% arm, values of 84%, 85%, 86% and 87% will be reconverted to a single value of 84%. This is a result of having the displayed values return to non-skewed SpO2 values at < 84% and > 96%, a safety design felt to be important by all involved in this trial (See Attached file USCD1). Thus the percentages reported to the DSMC for some of the ranges that include these values were not an accurate representation of the true values. However all values > 96% and < 84% are actual and do not require any conversion.

Percent of time of spent at SpO2 < 84% and > 96%
(RTI, Nov 29, 2005, 14:00 Hrs)

Range **Assigned**	High target (91-95)	Low target (85-89)
< 84%	8.51	16.62
> 96%	22.69	13.60

In the current SUPPORT study, an initial analyses utilizing only unaltered SpO2 values as shown above , ie those below 84% and above 96%, have shown that one arm had an SpO2 > 96% for 13.6% versus 22.69% of the time for the comparison arm, and the duration of an SpO2 < 84% was also different at 16.62% versus 8.51%. The values for SpO2s > 96% using unaltered data suggests that the SUPPORT trial to date has, if anything, reduced the duration of higher oxygen saturations.

In addition, analyses using only actual SpO2 demonstrate that the infants in this trial who are receiving supplemental oxygen are spending approximately 70% of the time with a true SpO2 value between 84% and 96%. We believe that this is information is very encouraging.

3. Impact of inclusion of data from periods in room air on saturation distributions:

As part of the SUPPORT trial, we collect information about inhaled oxygen concentration 3 times a day for the first 14 days and daily thereafter. We believe that an improved documentation of the times when infants are on room air will allow us to determine the saturations during actual oxygen exposure. At the present an infant is considered to be receiving supplemental oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized as receiving supplemental oxygen for significant periods when they are actually in room air. This would result in durations of SpO2 greater than 95% that were felt to be modifiable and reported as such when in fact there is no effective treatment for such elevated SpO2s. In addition, we do not know if such SpO2s on room air are associated with any morbidity. From the SUPPORT study data analyses to date we know that infants in room air have SpO2s > 95% for 46% to 69% of the time.

In view of this design, we would suggest that all future interval analyses for safety examine the ranges of <84% and >96% as those ranges that are considered to be low and high.

We believe that the SUPPORT trial will actually define the periods of time that ELBW infants spend with different ranges of SpO2, and that it is essential to collect this information. In addition, as our findings indicate a lower true percent of the time at SpO2 values >95%, and lower median SpO2 values than has previously been reported, we are in fact, reducing the time with high SpO2 values compared to usual care. The SUPPORT trial carefully evaluates risks, and we will be evaluating group differences for all important short and long term outcomes.

The SUPPORT trial methodology actively encourages all caretakers to keep SpO2 < 96% by having alarm limits set at 85% and 95%. These limits were utilized because it was felt that these represented current practice. The oximetry algorithms were designed to keep infants in the narrower target range of 88% to 92% with the realization that setting alarm limits at these values would severely increase the frequency of the alarms sounding. Nevertheless, our results to date suggest that we have decreased the expected percent of time > 95%, and in one group the value of 14% may be as low as is achievable in an actual clinical environment given the evidence provided by Hagadorn et al and Nghiem et al.

We believe the SUPPORT study will define the distribution and durations of pulse oximetry values among premature infants in highly staffed, dedicated academic centers, and among infants randomized to two different target ranges. For this reason alone, the SUPPORT trial will be very valuable. All of the procedures outlined below in response to your second concern will also allow us to further increase the percentage of time that the infants are in the maximally altered SpO2 ranges which we believe will further increase separation of these groups.

Response to Issue Number 2

There is concern that we have not achieved adequate separation by the current oximeters and study personnel.

1. As described above, the results of additional analyses performed in response to the concerns of the DSMC show differences in the durations of low and high SpO2s between the 2 oximeter groups. A careful analysis of the most recent converted values demonstrates that the cumulative time spent with an SpO2 of 90% or less is 24.3% (91% - 95%) versus 43% (85% - 89%), for the 2 oximeter groups, supporting the ability of the altered oximeters to produce differential SpO2 exposures.

2. We do acknowledge that it would be desirable to increase the percentage of time in the narrower target range and towards this end would propose the following changes to SUPPORT:

A. We will require **documentation that the alarm limits are set and functional as per protocol every 4-6 hours**. We have found that in some units the high alarms are being turned off, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned to the most appropriate personnel in each unit, which may include bedside or research nurses or respiratory therapists, and this procedure is already being done in many NRN units.

B. We will immediately initiate a **change in our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect saturations measured while on oxygen therapy and exclude saturations of infants in room air.** We will change the data form to indicate that the infant was either in oxygen for the entire 24 hours, and if not, will provide a more accurate estimate of the true time in oxygen, and we will continue with this form of data collection for the entire time that the infant is receiving oxygen. In the current protocol we collect such information 3 times a day for the first 14 days only and then daily thereafter. We believe that more frequent and extended documentation will allow us to determine more accurately the actual time that an infant is in room air. At the present the infant is considered to have spent a day in oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized in oxygen for significant periods when they are in room air. While in room air, we cannot manipulate the SpO2, and thus knowledge of the true time in oxygen will produce a more accurate representation of oximetry results that are subject to care interventions.

C. We will initiate **further training and in-service at all the sites to stress the importance of keeping the SpO2 alarms functional and at the limits of 85% and 95%**. In the past these were guidelines, and we will now change the study manual and protocol to indicate these limits are now set by protocol and that violations will be documented. We will encourage all caretakers to aim for an SpO2 value of 90% and make every effort to educate caretakers to make smaller adjustments in FiO2 and ensure that the infant is maintained between the 87% to 93%, the range with the maximal separation of the study oximeters. We will further facilitate the use of the 2 hour and 12 hour histograms showing the infants' actual ranges to provide feedback to the caretakers regarding the percentage of time in the target ranges.

D. We will develop **guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation**. More modulated increases in oxygen during these desaturation events will minimize overshoot and the potential of high SpO2 values. We would hope that such changes – ie increasing the FiO2 in steps of 5% as opposed to much larger increases will decrease the resultant overshoots creating the high SpO2 values. This will be included in the revised manual of operations.

E. **We will place bedside cards to indicate the target range**.

F. We will **initiate compliance monitoring visits coordinated by RTI to visit random sites**. These visits had been planned, but had not yet been initiated. The teams will consist of a member of RTI and a study coordinator, and they will review the adherence to the protocol and any other relevant issues.

G. We would recommend that at a minimum, the unblinded oximetry data be reviewed again after an additional 100 to 150 infants have been enrolled in this trial.

We thank the DSMC for their thoughtful concerns. We trust that our plans to move forward with the SUPPORT trial are acceptable to the DSMC. We are anxious to initiate the above changes, seek IRB approvals and re-activate this trial.

LATE BREAKER ABSTRACT SUBMISSION FORM

Abstracts and Payment must be RECEIVED by March 1, 2004

~ Abstracts must be submitted electronically using this form.
~ Abstracts, inclusive of title, authors, institutions, and graphs/tables, must fit in a 6.5 inch x 4 inch space between the two lines (appx. 2,600 characters). Use a font no smaller than 10 pt.
~ You must complete all information and include payment ($50 US) for your abstract to be considered.

Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation

J Hagadorn [1,2], A Furey [1], TH Nghiem [1], S Greene [1], E Abban [1], J Cho [1], P Shrestha [1], A Vora [1], M Landa [2], C Schmid [2], P Hibberd [2], CH Cole [1] and The AVIOx Study Group. [1]Div Newborn Med and [2]Div of Clin Care Research, Tufts-New England Med Ctr, Boston, MA.

Background: Detailed data are not available regarding the actual versus intended SpO2 in infants born <28 weeks gestation (extremely premature newborns, EPNs) in the neonatal period during routine care. **Objective:** To document actual SpO2 in EPNs in the first 4 weeks of life during routine care and compare to the level recommended by local policy/guideline. **Design/Methods:** EPNs <96 hours old were enrolled in a prospective multicenter cohort study. Oximetry data were collected every 2 seconds with masked signal-extraction oximeters for 72 hours in each of the first four weeks of life. Data were compared to SpO2 range prescribed by local institutional policy. **Results:** 14 centers from 3 countries enrolled 78 infants with mean birth weight 863 g (SD 208 g) and mean gestational age 26 wk (SD 1.4 wk). Lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for median of 70 hours (25^{th}-75^{th} percentiles 67-71 hr) in each week. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25^{th}-75^{th} percentiles 91-97; range of study center medians 91-96). Centers ranged between 16-71% compliance with intended SpO2 range. Most noncompliance was above intended range. **Conclusions:** Compliance with intended SpO2 range during routine care varied substantially among participating centers, and was generally poor regardless of intended level. These data will assist quality improvement and education efforts, and will aid planning of prospective randomized trials examining level of oxygenation. **Disclosure:** Funded by the SPR Student Research Program; Fight for Sight/Prevent Blindness America; The Tufts-NEMC Research Fund; GCRC/Natl Center for Research Resources MO1-RR00054, and NEI K23 EY/HD00420. Oximeters provided by Masimo Corp.

Briefly describe the reason why the December deadline could not be met:
Study still in progress at December deadline, with only about 60% of enrollment achieved.

Person to whom all communication should be addressed: James Hagadorn, MD

Complete Mailing Address: 750 Washington Street, Tufts-NEMC #44
Boston, MA 02111 USA

Telephone: 617.636.4193 Facsimile: 617.636.1456

Email: jhagadorn@tufts-nemc.org

First Author is a member of: __ APS __SPR __APA __ASPHO __ASPN __LWPES

Conflict of Interest/Disclosure Statement/Approval of All Authors

Work submitted for presentation must include an acknowledgement of funding sources of commercial nature and/or consulting or holding of significant equity in a company that could be affected by the results of the study. The intent of this policy is not to prevent a speaker with a potential conflict of interest from making a presentation, it is merely intended that any potential conflict should be identified openly so that the listeners may form their own judgments about the presentation with the full disclosure of the facts. *Even if indicated elsewhere in the abstract, this must appear as the last sentence of the abstract and read "funded by..." and/or "equity in..." if pertinent.*

By emailing this electronic file, you verify that: You have the approval of all authors to submit this work for presentation; this work will not have been previously published in manuscript format; any animal studies conform with the "Guiding Principles in the Care and Use of Animals" of the American Physiological Society and any human experimentation has been conducted according to a protocol approved by the institutional committee on ethics of human investigation or if no such committee exists, that it conforms with the principles of the Declaration of Helsinki of the World Medical Association (CLINICAL RESEARCH 14:193, 1966)

Signature of First Author, attesting to the above: _____

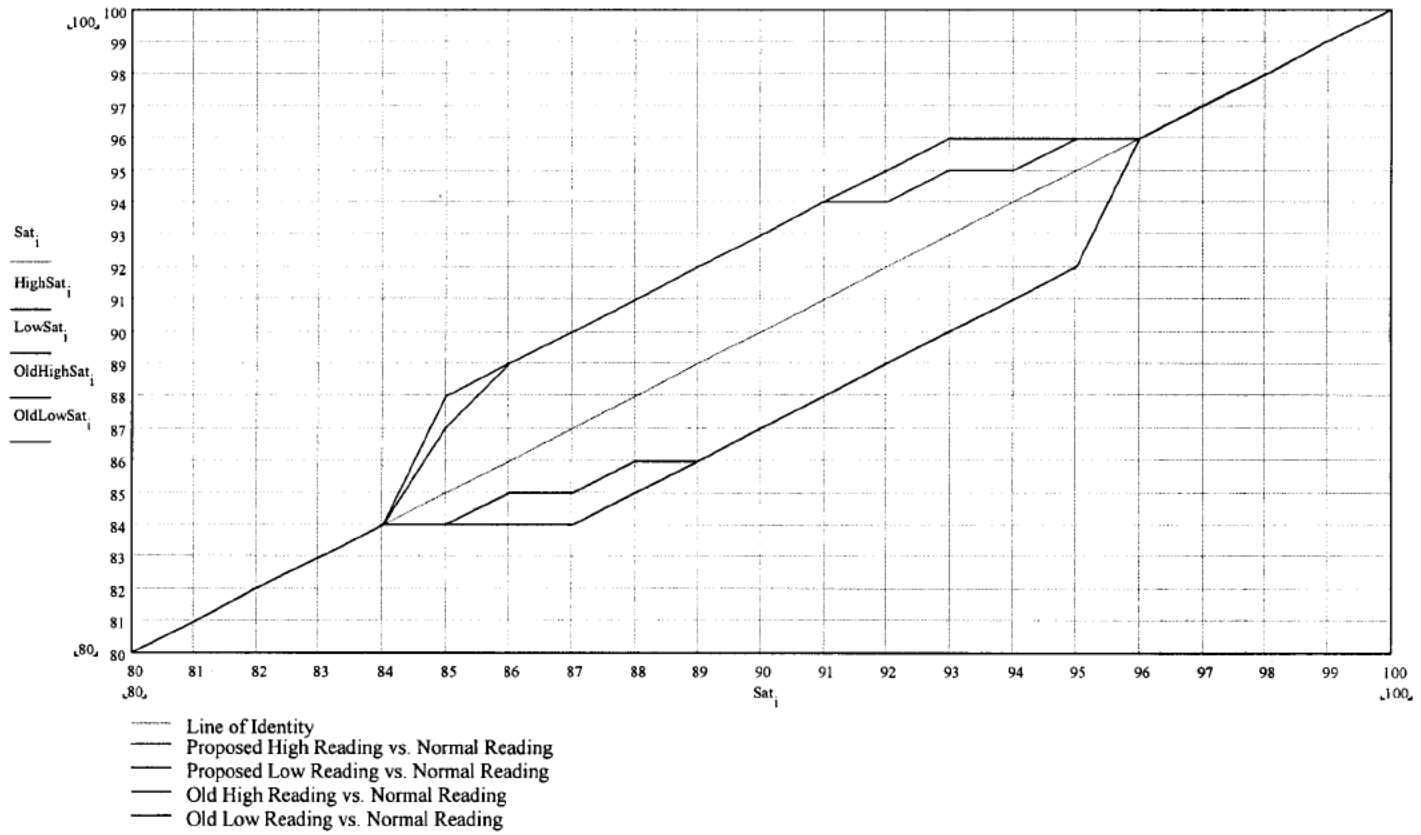
Final Submission Steps:

- Attach this file to an email and send to: datwood@aps-spr.org
- Fax a copy of this form to PAS Late Breakers, 281-419-0082 along with your payment form

Questions? Call, 281-419-0052

Converting Actual Readings to Low and High Readings

Actual Reading	To Low Reading	To High Reading
100	100	100
99	99	99
98	98	98
97	97	97
96	96	96
95	92	96
94	91	96
93	90	96
92	89	95
91	88	94
90	87	93
89	86	92
88	85	91
87	84	90
86	84	89
85	84	88
84	84	84
83	83	83
82	82	82
81	81	81
80	80	80
etc	etc	etc



The Low, Actual & High Reading oximeters synchronize for values greater than or equal to 96 % and less than or equal to 84 %.

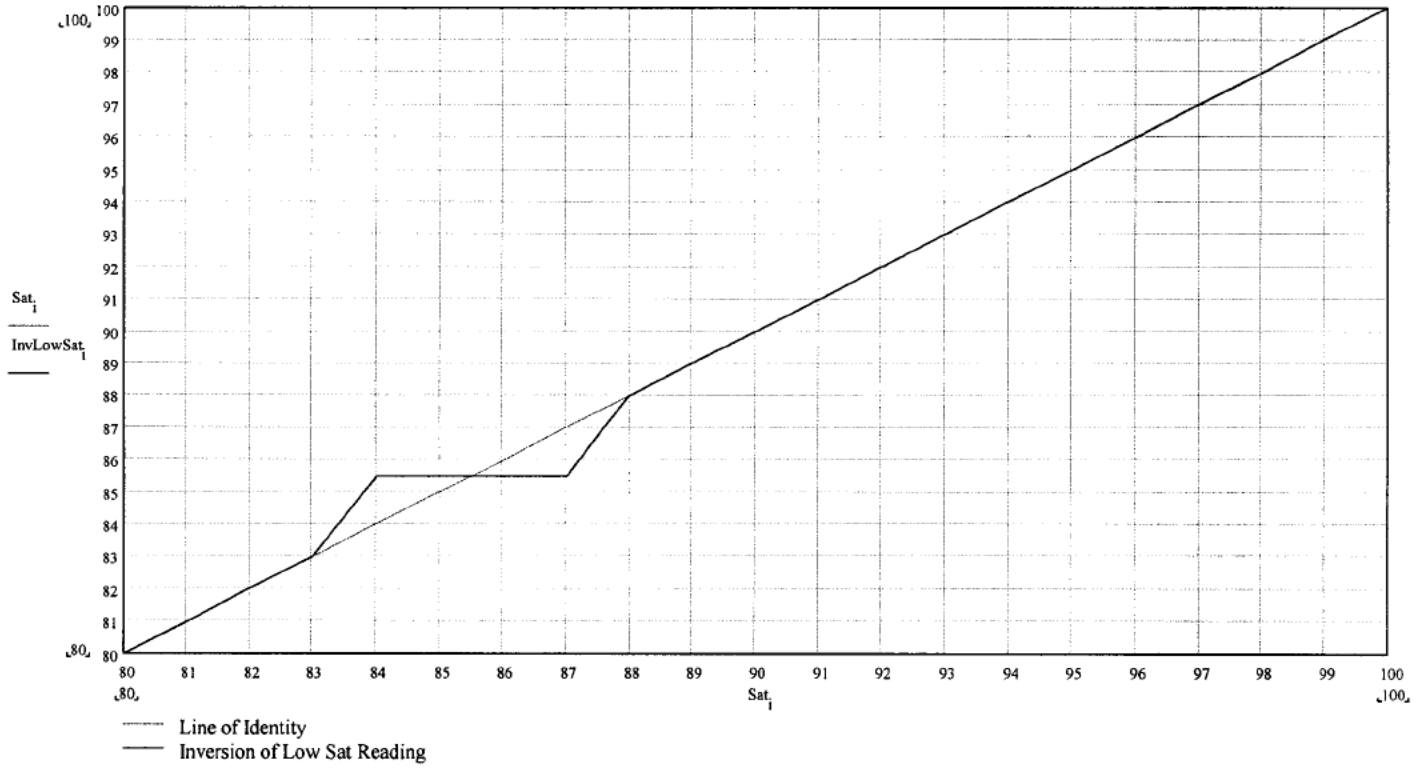
In the Actual range of 87 % to 95 %, the Low Reading Oximeter displays a value 3 points below actual.

In the Actual range of 85 % to 93 %, the High Reading Oximeter displays a value 3 points above actual.

Converting Low Readings to Normal Readings

Low Reading	To Normal Reading
100	100
99	99
98	98
97	97
96	96
95	95.75
94	95.50
93	95.25
92	95
91	94
90	93
89	92
88	91
87	90
86	89
85	88
84	85.5
83	83
82	82
81	81
80	80
etc	etc

Applying the above inversion yields the following performance:

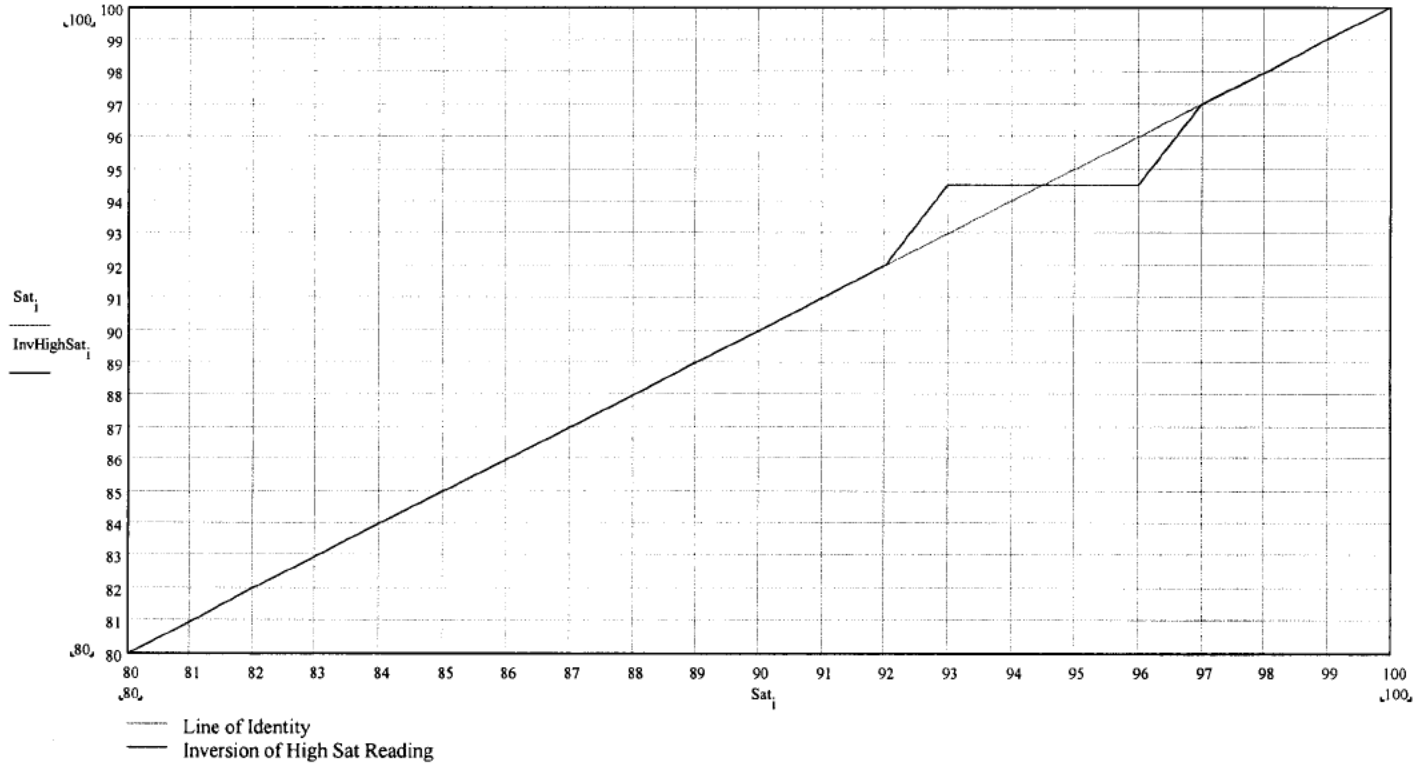


The inversion has no error above and below an actual reading of 88 % and 83 %, respectively. In between these limits, the inversion error does not exceed 1.5 %. Subjects are typically kept in the region of 91 % (88 % + 3 %) to 95 % (92 % + 3 %).

Converting High Readings to Actual Readings

High Reading	To Actual Reading
100	100
99	99
98	98
97	97
96	94.5
95	92
94	91
93	90
92	89
91	88
90	87
89	86
88	85
87	84.75
86	84.50
85	84.25
84	84
83	83
82	82
81	81
80	80
etc	etc

Applying the above inversion yields the following performance:



The inversion has no error above and below an actual reading of 97 % and 92 %, respectively. In between these limits, the inversion error does not exceed 1.5 %. Subjects are typically kept in the region of 85 % (88 % - 3 %) to 89 % (92 % - 3 %).

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November 30, 2005

Gordon Avery, M.D.
Chairman of the Data Safety Monitoring Committee
NICHD Neonatal Research Network

Dear Dr. Avery,

The SUPPORT Trial Subcommittee and the NICHD Network Steering Committee have reviewed in detail the concerns of the Data Safety Monitoring Committee. We are appreciative of the diligence and thoughtfulness that went into these concerns and we have carefully considered the comments made by the Data Safety Monitoring Committee with respect to both the issue of patient safety and the question of futility relative to the separation of the infants in the two oximetry arms of the trial.

We are very mindful of the need to protect patient safety and toward this end have reviewed the current experience relative to exposure of current ELBW infants to saturations above 95%. There is little information regarding this issue in the literature. We have quoted what we believe to be the relevant recent experiences, including the Network experience with exposures to higher SpO2 ranges. In addition we had asked RTI to provide us with unaltered oximetry data which allows us to look at information for oxygen saturations of 97% or greater and less than 84%, as these values were not altered by the algorithm in place for the study. We also compared the mean and median values of the SpO2 seen in the SUPPORT trial to date with those reported by Hagadorn et al, the only other report that contains such information. This information suggests that our current SpO2 exposures, especially to SpO2 values of 97% and above, for infants within the SUPPORT trial are probably less than is currently being experience outside of the trial, both from the Network experience and in the general practice of neonatology for the ELBW infant. In addition our median SpO2 values for both of our oximetry groups are lower than those reported by Hagadorn et al.

We agree that we should aim for greater separation between the oximetry groups, and are pleased that we are seeing some differences on SpO2 exposure between the groups. I have detailed our responses to each of the DSMC's concerns in the attached review. We believe that with these changes to the Protocol and Manual of operations and additional in-service at the sites coupled with intermittent site visits, that we will attain an even greater SpO2 separation and differential oxygen exposure for our 2 study groups. We would also like to recommend a re-evaluation of this data after an additional 100-150 infants have been enrolled.

We thank you and your committee for your careful review and suggestions. We hope that our responses are appropriate and that we may be allowed to continue this important trial

Sincerely,

Neil N. Finer, M.D.
Principal Investigator on behalf of the SUPPORT Subcommittee

Percent of time spent at each SpO2 value
(Includes 58 infants – 41 in High target group, 17 in Low target group)

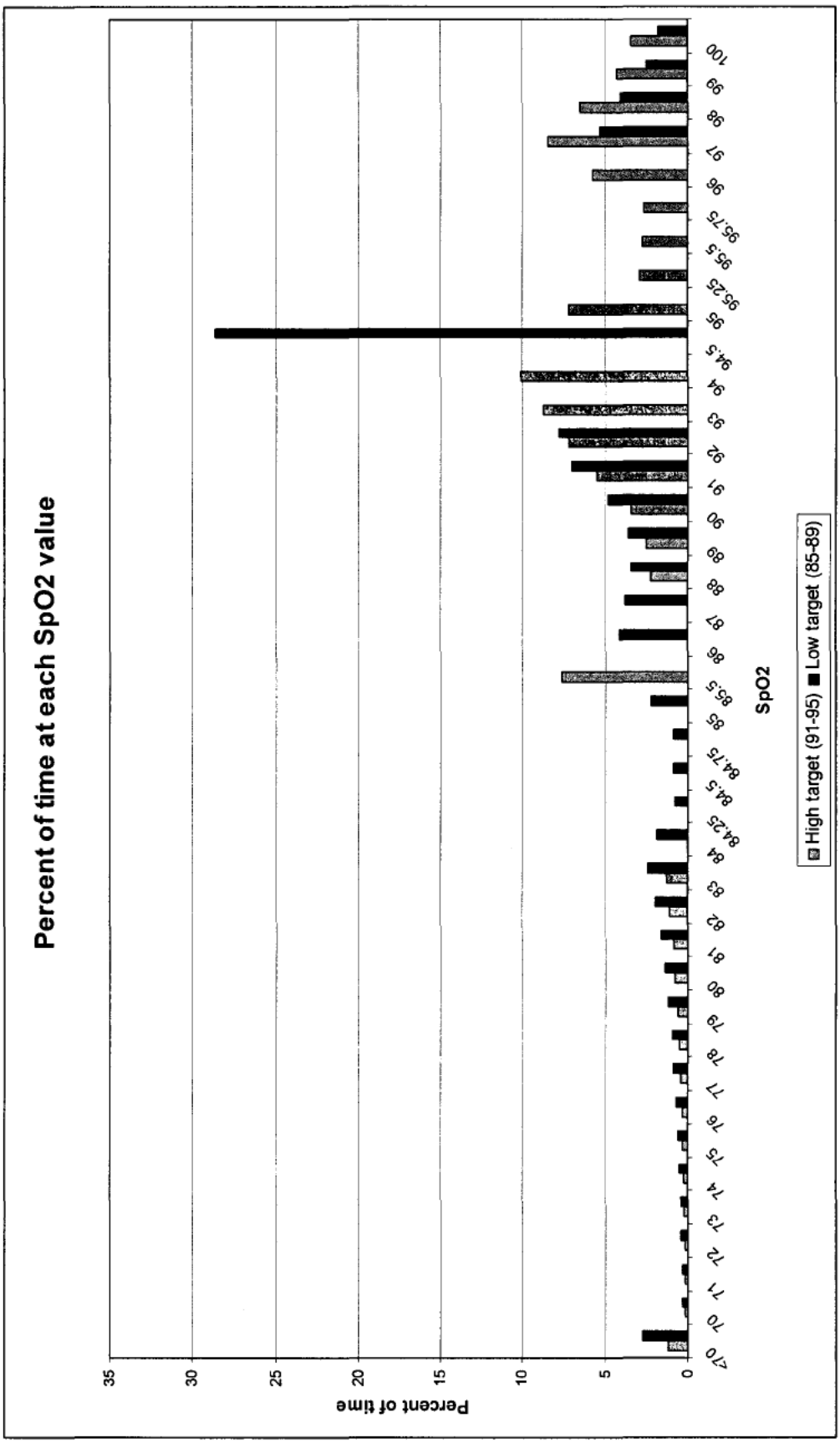
	High target (91-95)		Low target (85-89)	
SpO2	Percent	Cumulative	Percent	Cumulative
<70	1.20	1.20	2.73	2.73
70	0.14	1.34	0.31	3.04
71	0.17	1.51	0.37	3.40
72	0.20	1.71	0.41	3.82
73	0.23	1.94	0.47	4.29
74	0.27	2.21	0.54	4.83
75	0.31	2.52	0.62	5.45
76	0.37	2.89	0.72	6.17
77	0.44	3.33	0.84	7.00
78	0.53	3.86	0.97	7.98
79	0.62	4.48	1.17	9.14
80	0.74	5.22	1.39	10.53
81	0.90	6.12	1.65	12.17
82	1.08	7.20	2.01	14.18
83	1.30	8.51	2.43	16.62
84	0.00	8.51	1.92	18.53
84.25	0.00	8.51	0.79	19.33
84.5	0.00	8.51	0.84	20.17
84.75	0.00	8.51	0.88	21.05
85	0.00	8.51	2.20	23.25
85.5	7.60	16.11	0.00	23.25
86	0.00	16.11	4.12	27.37
87	0.00	16.11	3.80	31.17
88	2.25	18.36	3.40	34.57
89	2.52	20.89	3.61	38.18
90	3.43	24.32	4.81	42.99
91	5.50	29.82	7.00	49.99
92	7.22	37.04	7.76	57.76
93	8.79	45.83	0.00	57.76
94	10.10	55.94	0.00	57.76
94.5	0.00	55.94	28.64	86.40
95	7.23	63.17	0.00	86.40
95.25	2.95	66.12	0.00	86.40
95.5	2.75	68.86	0.00	86.40
95.75	2.68	71.55	0.00	86.40
96	5.76	77.31	0.00	86.40
97	8.46	85.76	5.31	91.71
98	6.52	92.28	4.01	95.72
99	4.26	96.54	2.51	98.23
100	3.46	100.00	1.77	100.00

Median SpO2

	High target (91-95)	Low target (85-89)
Median	94	92

Percent of time of spent at SpO2 0-83 and 97+

Range	High target (91-95)	Low target (85-89)
0-83	8.51	16.62
97+	22.69	13.60



From: Das, Abhik
To: Hastings, Betty J.; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie; Schaefer, Scott E.; Poole, W. Kenneth
Subject: RE: DSMC SUPPORT Conference Call
Date: Friday, December 02, 2005 9:23:21 AM

We will have all the analysis of the pulse ox data ready by late Monday for all kids in SUPPORT. We plan to send this to Neil at that time. He can then update his response to the DSMC with the latest numbers, which, if current trends hold, will make it stronger. So, I think we may want to hold off on sending this to the DSMC until then.

Thanks

Abhik

-----Original Message-----
From: Hastings, Betty J.
Sent: Friday, December 02, 2005 9:06 AM
To: 'Higgins, Rosemary (NIH/NICHD)'
Cc: Das, Abhik
Subject: RE: DSMC SUPPORT Conference Call

Yes, I believe Neil sent them. I'll plan to send them the following:
Agenda and list of participants
List of members with their specialty, etc.
SUPPORT Protocol
Letter of Response from the Steering Committee
The two abstracts.

Anything else?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 02, 2005 9:00 AM
To: Hastings, Betty J.
Subject: RE: DSMC SUPPORT Conference Call

The PI's had until last night to weight in – Neil will do it today.

Can we also send the Hagadorn abstract and the Case Western Abstract to them? Do you have the files for both?
Thanks
Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Friday, December 02, 2005 8:58 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: DSMC SUPPORT Conference Call

Do you know when the letter will be ready to send out to the DSMC?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 02, 2005 8:56 AM
To: Hastings, Betty J.
Subject: RE: DSMC SUPPORT Conference Call

Yes,
Neonatology, bioethics

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Friday, December 02, 2005 8:55 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: DSMC SUPPORT Conference Call

Thanks so much. Do you have this for Robert Boyle?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 02, 2005 8:54 AM
To: Hastings, Betty J.
Subject: RE: DSMC SUPPORT Conference Call

Avery – Neonatology, Clinical trials
D'Alton – Obstetrics, maternal fetal medicine, antenatal screening
Gleason- Neonatology, cerebral-vascular physiology
Carol Redmond – biostatistics
Marian Willinger – control of breathing, SIDS

Merrin Tompson – Neonatology, Respiratory physiology
Carl Hunt – Neonatology, Sleep, sleep apnea
Marilee Allen – Neonatology, high risk infant follow up, neurodevelopment

---

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Friday, December 02, 2005 8:41 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: FW: DSMC SUPPORT Conference Call

Rose,
Could you help me with this? The DSMC members could also be characterized as to specialty. I not sure that I have this.
Thank you.
Betty
-----Original Message-----
From: Gordon Avery [mailto[redacted](b) (6)]
Sent: Friday, December 02, 2005 8:35 AM
To: Webb, Robin E.
Cc: Hastings, Betty J.
Subject: Re: DSMC SUPPORT Conference Call

I have the Dec 13 call on my calendar. Please send, ahead of time, the current roster of DSMC Committee, NIH rep, RTI major players, with e-mail and phone numbers. The DSMC members could also be characterized as to specialty. This will aid us all in being present to one another under the current practice of no meetings, all conference calls. In light of what we will be discussing, we should also have, in advance of the call, the SUPPORT protocol and the Steering Committee proposal for continuing, if there is such. We need to do reading and thinking in advance of the call. Thanks. Gordon

----- Original Message -----
From: Webb, Robin E.
To: cgleason@u.washington.edu ; ckr3+@pitt.edu ; gavery123@hotmail.com ;

md511@columbia.edu ; [SCRN] Willinger, Marian ; rjb6j@hscmail.mcc.viriginia.edu ; huntc@nhlbi.nih.gov ; mcallen@jhmi.edu ; merran.thomson@ic.ac.uk ; nfiner@ucsd.edu ; Das, Abhik ; Poole, W. Kenneth
Cc: csd12@columbia.edu ; mck6@pitt.edu ; milhil@u.washington.edu ; poppoff@u.washington.edu ; Hastings, Betty J.
Sent: Friday, December 02, 2005 7:57 AM
Subject: DSMC SUPPORT Conference Call

The DSMC SUPPORT conference call is scheduled for Tuesday, December 13 from 2pm-3:30pm ET. An email with all the details will be sent out soon.

Thanks,
Robin

Robin Webb
RTI International
6110 Executive Blvd., Suite 902
Rockville, MD 20853
301-770-8204

From:	Neil Finer
To:	"Abbot Laptook"
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Subject:	RE: Response to DSMC Steering Nov 30 05
Date:	Thursday, December 01, 2005 8:54:58 PM
Attachments:	Percent of time spent at each SpO2 value.doc

Hi Abbot
We are all concerned about any more data collection and our present solution is to declare a day an oxygen or room air day based on the greater percentage of time in oxygen for that day. I also agree that while we want more FiO2 data, I think RTI already feels overloaded with the oximeter data. We did discuss changing the alarms to lower than 84% and higher than 95% but most feel that the current range is most acceptable.
In addition, we do have some separation in the SpO2 exposures of the 2 oximeter groups. More would be better and all of our efforts should help that. I do not know how much more we need. If one calculates the differences that we are currently seeing, then in a given day the infants in 1 arm of the study are spending 18% more time with an SpO2 less than 90% than the other group, that represents about 4 hours per day. The same group also spends about 9% less of the time with an SpO2 above 97%.
I know that you have an interest in this data and so I am sending you the additional data that we had run and about 60 babies. RTI could not do more babies as this tied up all their computers.
I have not shared this outside the Subcommittee so as not to get everyone possibly more confused.
We do have differences, and more is probably better, but we are creating 2 different SpO2 exposures.
Thanks for sharing your concerns Abbot
Be well
Neil

From: Abbot Laptook [mailto:ALaptook@WIHRI.org]
Sent: Thursday, December 01, 2005 5:40 PM
To: nfiner@ucsd.edu
Cc: HigginsR@mail.nih.gov
Subject: RE: Response to DSMC Steering Nov 30 05

Neil
I agree with the document that you have very nicely put together but I am still concerned that the additional data to collect (issue 2, number 2) to determine whether infants are in oxygen or room air will not be sufficiently accurate. At least at Brown and Parkland the FiO2 is recorded hourly and obviously tells little about how much oxygen they are in for time intervals inbetween these documentations. I think this issue needs to be considered further since I am afraid that you will still be lumping infants in room air with infants in oxygen. Secondly I have real concerns that we can adequately keep these infants in the goal ranges desired given their lability; should there be consideration to wider goal ranges for each group? Abbot

---

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, December 01, 2005 2:40 PM
To: 'Richard Ehrenkranz'; 'Higgins, Rosemary (NIH/NICHD)'; Abbot Laptook; 'Abhik Das'; 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; 'Charles Rosenfeld'; 'Dale Phelps'; 'Ed Donovan'; 'Jobe Alan (E-mail)'; 'Lemons Jim (E-mail)'; 'Michael O'Shea'; 'Michelle Walsh'; 'Oh William (E-mail)'; 'Poole Kenneth (E-mail)'; 'Ronald GOldberg'; 'Shahnaz Duara'; 'Shankaran Seetha (E-mail)'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; walid.salhab@utsouthwestern.edu
Cc: 'Petrie, Carolyn'
Subject: RE: Response to DSMC Steering Nov 30 05

Thanks Richard
I have made the clarifications

Corrected Hagadorn et al to 2004 and the n=78 and clarified for each of the 4 weeks. And I have stated for greater than 2 hours
In answer to your question – any oxygen more than 2 hours is a yes for oxygen after 14 days
The next query – I have clarified the actual groups and yes, these were additional data runs that we asked RTI to perform
". As described above, the results of additional analyses performed in response to the concerns of the DSMC show differences in the durations of low and high SpO2s between the 2 oximeter groups. A careful analysis of the most recent converted values demonstrates that the cumulative time spent with an SpO2 of 90% or less is 24.3% (91% - 95%) versus 43% (85% - 89%), for the 2 oximeter groups, supporting the ability of the altered oximeters to produce differential SpO2 exposures."
#4- I have changed that to read ".We have found that in some units the high alarms are being turned off, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned to the most appropriate personnel in each unit, which may include bedside or research nurses or respiratory therapists, and this procedure is already being done in many NRN units"

We added "to have spent a day" as you suggested.
Many thanks to you and tour team for these suggestions
Be well
Neil

From: Richard Ehrenkranz [mailto:richard.ehrenkranz@yale.edu]
Sent: Thursday, December 01, 2005 6:17 AM
To: Higgins, Rosemary (NIH/NICHD); alaptook@WIHRI.org; Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@utsouthwestern.edu
Cc: Petrie, Carolyn; richard.ehrenkranz@yale.edu
Subject: Re: Response to DSMC Steering Nov 30 05

Hi,
This is an excellent response to the DSMC. Our SUPPORT team has reviewed it and finds it acceptable. I have several minor comments/revisions to offer:
1. Hagadorn's PAS abstract is from 2004 not 2005; at least the version that was sent with the materials indicated 2004. Also in discussion about that abstract, revise the sentence to indicate that the infants were monitored for 72 hrs each week during the first 4 weeks. The current sentence is unclear. Finally, the abstract refers to 78 infants not 72 infants.
2.Response 1, paragraph 6, sentence 3: This sentence is confusing. Does this mean that supplemental oxygen for > 2 hrs on a day led to classifying that day as a day in oxygen?
3. Response 2, paragraph 1, sentence 3: I found this sentence confusing. Can you simplify it and make it clear to which groups the cumulative times are assigned? Also do these values refer to the values included in the DSMC report or to other calculations? That was not clear to me.
4. Response 2, #1: Why must that task be assigned to RTs? I suggest that you make this a little more flexible, since RTs may not be involved in setting alarm limits in some units. Research nurses at Yale have performed that task for this trial. 5.Response 2, #2, sentence 5: I suggest the following revision to this sentence;""At the present the infant is considered to

have spent a day in oxygen if....

I hope these minor comments are helpful.
Richard

At 11:22 AM 11/30/2005, Higgins, Rosemary (NIH/NICHD) wrote:

HI,
Attached is the final response to the DSMC as discussed on the phone this morning. Please review this and let me know by tomorrow (December 1) evening if this is acceptable to you and your site.
A special thanks to Neil and RTI (Marie and Abhik) for all the time and effort that has been put into this project!!
Rose
<<Response to DSMC Steering Nov 30 05.doc>>

Percent of time spent at each SpO2 value
(Includes 58 infants – 41 in High target group, 17 in Low target group)

	High target (91-95)		Low target (85-89)	
SpO2	Percent	Cumulative	Percent	Cumulative
<70	1.20	1.20	2.73	2.73
70	0.14	1.34	0.31	3.04
71	0.17	1.51	0.37	3.40
72	0.20	1.71	0.41	3.82
73	0.23	1.94	0.47	4.29
74	0.27	2.21	0.54	4.83
75	0.31	2.52	0.62	5.45
76	0.37	2.89	0.72	6.17
77	0.44	3.33	0.84	7.00
78	0.53	3.86	0.97	7.98
79	0.62	4.48	1.17	9.14
80	0.74	5.22	1.39	10.53
81	0.90	6.12	1.65	12.17
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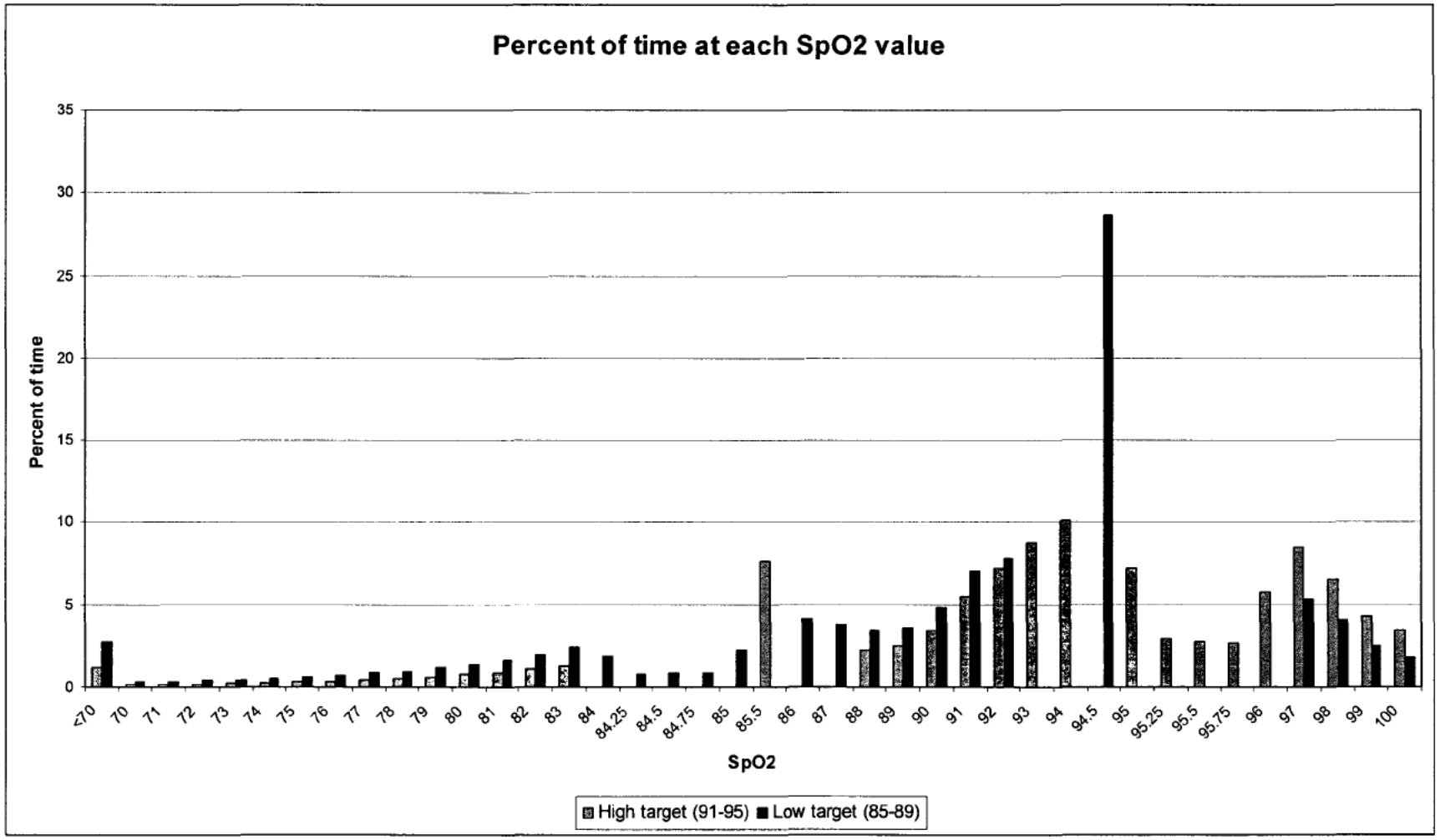
83	1.30	8.51	2.43	16.62
84	0.00	8.51	1.92	18.53
84.25	0.00	8.51	0.79	19.33
84.5	0.00	8.51	0.84	20.17
84.75	0.00	8.51	0.88	21.05
85	0.00	8.51	2.20	23.25
85.5	7.60	16.11	0.00	23.25
86	0.00	16.11	4.12	27.37
87	0.00	16.11	3.80	31.17
88	2.25	18.36	3.40	34.57
89	2.52	20.89	3.61	38.18
90	3.43	24.32	4.81	42.99
91	5.50	29.82	7.00	49.99
92	7.22	37.04	7.76	57.76
93	8.79	45.83	0.00	57.76
94	10.10	55.94	0.00	57.76
94.5	0.00	55.94	28.64	86.40
95	7.23	63.17	0.00	86.40
95.25	2.95	66.12	0.00	86.40
95.5	2.75	68.86	0.00	86.40
95.75	2.68	71.55	0.00	86.40
96	5.76	77.31	0.00	86.40
97	8.46	85.76	5.31	91.71
98	6.52	92.28	4.01	95.72
99	4.26	96.54	2.51	98.23
100	3.46	100.00	1.77	100.00

Median SpO2

	High target (91-95)	Low target (85-89)
Median	94	92

Percent of time of spent at SpO2 0-83 and 97+

Range	High target (91-95)	Low target (85-89)
0-83	8.51	16.62
97+	22.69	13.60



From: Berberich, Mary Anne (NIH/NHLBI) [E]
Subject: SUPPORT
Date: Thursday, December 01, 2005 4:07:33 PM

Hi Rose,

I am sending this E-mail, rather than just ringing you up because talking (b) (6) [redacted]. I can listen, so if it's easier for you to call back, please feel free.

(b) (5) [redacted] Could you clarify this issue?

Thanks,
Mary Anne

From: Neil Finer
To: "Hastings, Betty J."
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: letter
Date: Thursday, December 01, 2005 3:39:50 PM

I will make myself available and have blocked this on my calendar
Thanks Betty
Neil

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Thursday, December 01, 2005 9:49 AM
To: nfiner@ucsd.edu
Subject: RE: letter
Importance: High

Hi Neil,
I just thought I would take opportunity to ask you if you would be available at 2:00pm EST on December 13th?This seems to be a date that we can get the DSMC together.
Thanks a lot.
Betty

> -----Original Message-----
> **From:** Neil Finer [mailto:nfiner@ucsd.edu]
> **Sent:** Thursday, December 01, 2005 12:44 PM
> **To:** 'Higgins, Rosemary (NIH/NICHD)'; 'Phelps, Dale'
> **Cc:** 'D'Angio, Carl'; 'Avroy A. Fanaroff, M.D.'; Hastings, Betty J.; 'Ed Donovan'; Poole, W. Kenneth; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
> **Subject:** RE: letter
>
> Hi Carl Dale and Rose
> Thank you for your suggestions, all of which have been incorporated in the current revision. We do have a strategy if the decision is to close this arm. Rose and I have discussed this, and I would rather be hopeful that we can convince the DSMC that we be allowed to move ahead. If the DSMC decides to recommend that we close the oximetry arm on the basis of the concerns expressed to us, and the lack of any evidence, then I would ask I and any others who wish to accompany me be allowed to have a face to face meeting with the DSMC and Dr Alexander.
> There is no safety issue, and we do have a degree of separation. More would be unequivocally better, but there is no evidence that we have reached futility. We have not even analyzed the FiO2 data to determine if the 2 groups have different oxygen exposures. The Network needs to strenuously defend our ability to complete well designed and potentially useful trials from premature closure. I was involved the stopping of NINOS, (for efficacy, I was opposed as was Richard) and participated in PINO, (stopped without unequivocal evidence).
> For me, if the decision is to stop the oximetry arm on the basis of the current findings, the continuation of SUPPORT in its entirety at this time is an issue that I am prepared to go the distance on. I realize that this may not be the view of everyone, and I will bear that responsibility alone.
> Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, December 01, 2005 8:33 AM
To: Phelps, Dale; nfiner@ucsd.edu
Cc: D'Angio, Carl
Subject: RE: letter

I think we should see what happens with this response – if it is disapproved, we can cross the

ventilation arm bridge at that time.

Thanks
Rose

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Thursday, December 01, 2005 11:29 AM
To: "nfiner@ucsd.edu' '; Higgins, Rosemary (NIH/NICHD)
Cc: D'Angio, Carl
Subject: RE: letter

Hi Neil and Rose,

I'm catching up with the East Coast morning. Reading Carl's note below, I am reminded that the DSMC has called for a STOP to this trial. I am hopeful that we'll be persuavsive, but it is not a done deal.

Do we need to be preparing to move forward with only the two ventilation arms? Should that be mentioned in the letter? I have conflicting thoughts about that -- don't bring it up at this time probably. I think we'd rather not give them an 'easy path' and therefore we still should advocate for the full 2x2 study. (with all the cautions in our 'second issue' review.

Dale

-----Original Message-----
From: D'Angio, Carl
To: 'nfiner@ucsd.edu'
Cc: Phelps, Dale
Sent: 12/1/2005 9:40 AM
Subject: RE:

Neil,

The revised response looks good overall. I guess I'm more of a glass-half-empty person on this, but all the available data suggest to me that centers have so far been unable to comply with the protocol targets (particularly in the 85-89% group) and that the separation between groups is less than that achieved in other similar studies. I share the DSMB's concern that, without significant improvement in compliance to protocol, the oximetry comparison could be futile. As a result, the tone of the response to Issue #2 seems a bit too sunny to me, and I worry that the DSMB will view it as Pollyanna-ish. That being said, you've suggested all the appropriate steps to try to improve and monitor compliance, so I agree completely with the actions you lay out.

A couple of minor typographical things:

In Issue 2, B, I think you mean "either in or out of oxygen for the

entire 24 hours, and if not,...."

"Exposures" rather than "esxposures" in the letter.

All these comments are for your information only. Dale has the final vote from our center.

Thanks again for your work on this.

Carl

~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

Carl T. D'Angio, MD

Associate Professor of Pediatrics

Director, Pediatric Clinical Research Office

Division of Neonatology

Golisano Children's Hospital at Strong

University of Rochester Medical Center

601 Elmwood Avenue, Box 651

Rochester, NY 14642

Phone (585) 273-4911, Fax (585) 461-3614

carl_dangio@urmc.rochester.edu

~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 30, 2005 5:40 PM
To: 'Higgins, Rosemary (NIH/NICHD)'; 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
Cc: Phelps, Dale; D'Angio, Carl
Subject:

Hi Rose

Here is the current revision with the changes suggested by Dale, Carl, Shanaz, and Michele. Ron suggested a letter to the DSMC - I think this is a good idea, please review and see if I have set the correct tone.

I will respond further if I get further ideas. Thanks to everyone for their input.

Neil

From: Neil Finer
To: "Phelps, Dale"; Higgins, Rosemary (NIH/NICHD) [E]; ""Avroy A. Fanaroff, M.D." "; ""Betty Hastings" "; ""Ed Donovan" "; ""Ken Poole" "; ""Michele" "; ""Shahnaz Duara" "; ""Wade Rich" "; ""Wally Carlo" "
Cc: "D"Angio, Carl"; "Neil Finer"
Subject: RE:
Date: Wednesday, November 30, 2005 10:02:49 PM
Attachments: Response to DSMC final revised.doc
Avery Letter edits.doc

Thanks Dale
I have removed the "whoops" - should have been "an" not "and" and fixed the typos in the letter.
I'll wait till I receive any further edits.
Be well and thanks for the careful reading.
Neil

-----Original Message-----
From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, November 30, 2005 6:28 PM
To: 'Neil Finer '; "Higgins, Rosemary (NIH/NICHD)' '; "Avroy A. Fanaroff, M.D.' '; "Betty Hastings' '; "Ed Donovan' '; "Ken Poole' '; "Michele' '; "Shahnaz Duara' '; "Wade Rich' '; "Wally Carlo' '
Cc: D'Angio, Carl
Subject: RE:

Hi all,

As Carl said for us, I vote to go forward to the DSMC.

One whoops on the report and two typos in the letter provided.

Actually, since the letter is first draft and intended to be an 'Executive
Summary', I would shorten it more.
However Neil, EXCELLENT tone achieved!

Thank you so much!

Dalek Phelps

-----Original Message-----
From: Neil Finer
To: 'Higgins, Rosemary (NIH/NICHD)'; 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
Cc: Phelps, Dale; D'Angio, Carl
Sent: 11/30/2005 5:40 PM

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their input.

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<<Response to DSMC Steering Final.doc>> <<Avery Letter.doc>>

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Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

We have responded to each of these concerns and our responses are detailed below

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(RTI, Nov 29, 2005, 14:00 Hrs)

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assigned to the respiratory therapists, and this procedure is already being done in many NRN units.

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C. We will initiate **further training and in-service at all the sites to stress the importance of keeping the SpO2 alarm functional and at the limits of 85% and 95%**. In the past these were guidelines, and we will now change the study manual and protocol to indicate these limits are now set by protocol and that violations will be documented. We will encourage all caretakers to aim for an SpO2 value of 90% and make every effort to educate caretakers to make smaller adjustments in FiO2 and ensure that the infant is maintained between the 87% to 93%, the range with the maximal separation of the study oximeters. We will further facilitate the use of the 2 hour and 12 hour histograms showing the infants' actual ranges to provide feedback to the caretakers regarding the percentage of time in the target ranges.

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Neil N. Finer, M.D.
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Director, Division of Neonatology
Department of Pediatrics

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San Diego, CA 92103-8774
(619) 543-3759
Fax (619) 543-3812

November 30, 2005

Gordon Avery, M.D.
Chairman of the Data Safety Monitoring Committee
NICHD Neonatal Research Network

Dear Dr. Avery,

The SUPPORT Trial Subcommittee and the NICHD Network Steering Committee have reviewed in detail the concerns of the Data Safety Monitoring Committee. We are appreciative of the diligence and thoughtfulness that when into these concerns and we have carefully considered the comments made by the Data Safety Monitoring Committee with respect to both the issue of patient safety and the question of futility relative to the separation of the infants in the two oximetry arms of the trial.

We are very mindful of the need to protect patient safety and toward this end have reviewed the current experience relative to exposure of current ELBW infants to saturations above 95%. As you are well aware, there is little information regarding this in the literature. We have quoted what we believe to be the relevant recent experiences, including the Network experience with exposures to higher SpO2 ranges. In addition we had asked RTI to provide us with unaltered oximetry data which allows us to look at information for oxygen saturations of 97% or greater and less than 84%, as these values were not altered by the algorithm in place for the study. We also compared the mean and median values of the SpO2 seen in the SUPPORT trial to date with those reported by Hagadorn et al, the only other report that contains such information. This information suggests that our current SpO2 exposures, especially to SpO2 values of 97% and above, for infants within the SUPPORT trial are probably less than is currently being experience outside of the trial, both from the Network experience and in the general practice of neonatology for the ELBW infant. In addition our median SpO2 values for both of our oximetry groups are lower than those reported by Hagadorn et al.

We agree that we should aim for greater separation between the oximetry groups, and are pleased that we are seeing some differences on SpO2 exposure between the groups. I have detailed our responses to each of the DSMCs concerns in the attached review. We believe that with these changes to the protocol and Manual of operations and additional in-service at the sites coupled with intermittent site visits, that we will attain an even greater SpO2 separation and differential oxygen exposure for our 2 study groups. We would also like to recommend a re-evaluation of this data after an additional 100-150 infants have been enrolled.

We thank you and your committee for your careful review and suggestions. We hope that our responses are appropriate and that we may be allowed to continue this important trial

Sincerely,

Neil N. Finer, M.D.
Principal Investigator on behalf of the SUPPORT Subcommittee

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD) [E]; "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Cc:	"Phelps, Dale"; "D"Angio, Carl"
Date:	Wednesday, November 30, 2005 5:40:39 PM
Attachments:	Response to DSMC Steering Final.doc Avery Letter.doc

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NICHD Neonatal Research Network

Dear Dr. Avery,

The SUPPORT Trial Subcommittee and the NICHD Network Steering Committee have reviewed in detail the concerns of the Data Safety Monitoring Committee. We are appreciative of the diligence and thoughtfulness that when into these concerns and we have carefully considered the comments made by the Data Safety Monitoring Committee with respect to both the issue of patient safety and the question of futility relative to the separation of the infants in the two oximetry arms of the trial.

We are very mindful of the need to protect patient safety and toward this end have reviewed the current experience relative to exposure of current ELBW infants to saturations above 95%. As you are well aware, there is little information regarding this in the literature. We have quoted what we believe to be the relevant recent experiences, including the Network experience with esxposures to higher SpO2 ranges. In addition we had asked RTI provide us with unaltered oximetry data which allows us to look at information for oxygen saturations of 97% or greater and less than 84%, as these values were not altered by the algorithm in place for the study. We also compared the mean and median values of the SpO2 seen in the SUPPORT trial to date with those reported by Hagadorn et al, the only other report that contains such information. This information suggests that our current SpO2 exposures, especially to SpO2 values of 97% and above, for infants within the SUPPORT trial are probably less than is currently being experience outside of the trial, both from the Network experience and in the general practice of neonatology for the ELBW infant. In addition our median SpO2 values for both of our oximetry groups are lower than those reported by Hagadorn et al.

We agree that we should aim for greater separation between the oximetry groups, and are pleased that we are seeing some differences on SpO2 exposure between the groups. I have detailed our responses to each of the DSMCs concerns in the attached review. We believe that with these changes to the protocol and Manual of operations and additional in-service at the sites coupled with intermittent site visits, that we will attain an even greater SpO2 separation and differential oxygen exposure for our 2 study groups. We would also like to recommend a re-evaluation of this data after an additional 100-150 infants have been enrolled.

We thank you and your committee for your careful review and suggestions. We hope that our responses are appropriate and that we may be allowed to continue this important trial

Sincerely,

Neil N. Finer, M.D.
Principal Investigator on behalf of the SUPPORT Subcommittee

From:	Neil Finer
To:	"D"Angio, Carl"; Higgins, Rosemary (NIH/NICHD) [E]; alaptook@WIHRI.org; "Abhik Das"; "Brenda Poindexter"; "Carlo Waldemar (E-mail)"; "Charles Rosenfeld"; "Phelps, Dale"; "Ed Donovan"; "Ehrenkranz Richard (E-mail)"; "Jobe Alan (E-mail)"; "Lemons Jim (E-mail)"; "Michael O"Shea"; "Michelle Walsh"; "Oh William (E-mail)"; "Poole Kenneth (E-mail)"; "Ronald GOldberg"; "Shahnaz Duara"; "Shankaran Seetha (E-mail)"; "Stevenson David (E-mail)"; "Stoll Barbara (E-mail)"; "Tyson Jon (E-mail)"; walid.salhab@utsouthwestern.edu
Cc:	"Laroia, Nirupama"; vanmeurs@stanford.edu; "Avroy A. Fanaroff"; reverett@med.miami.edu; kurt.schibler@cchmc.org; ambal@uab.edu; "Morris, Brenda H"; "Michael Cotten"; Wade Rich; "Gantz, Marie"; "Petrie, Carolyn"
Subject:	RE: Response to DSMC Steering Nov 30 05
Date:	Wednesday, November 30, 2005 5:13:39 PM

Hi Carl
All great ideas! I will definitely add a re-evaluation after the next 100-150 infants at a minimum. I agree with you that the curves may show less separation than we want, and I would ague that we make changes to ensure better separation than we have achieved. Wally is our guru regarding best performance with oximeters, and we asking Wally to guide us in the education process to get better compliance.
Many thanks for these thoughtful comments
Neil

-----Original Message-----
From: D'Angio, Carl [mailto:Carl_Dangio@URMC.Rochester.edu]
Sent: Wednesday, November 30, 2005 1:50 PM
To: 'Higgins, Rosemary (NIH/NICHD)'; alaptook@WIHRI.org; Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Phelps, Dale; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@utsouthwestern.edu
Cc: Laroia, Nirupama; vanmeurs@stanford.edu; Avroy A. Fanaroff; reverett@med.miami.edu; kurt.schibler@cchmc.org; ambal@uab.edu; Morris, Brenda H; Michael Cotten; Wade Rich; Gantz, Marie; Petrie, Carolyn
Subject: RE: Response to DSMC Steering Nov 30 05

Dear Rose and Neil,

I have a few additional suggestions that I didn't have the opportunity to make before I needed to leave the call.

1. The response to "Issue #1" looks fine and addresses the issue cogently and completely.

2. The response to "Issue #2" is reassuring in that there is some separation between the groups. However, it's difficult for me to assess completely how similar or different the degree of separation is from those achieved in other studies (STOP-ROP and BOOST). From an empirical point of view, STOP-ROP appeared to have an offset of 5% of group medians (92% vs. 97%, at least for the median of the medians from Table 4 in the paper) and had a measurable physiologic effect. BOOST had an offset of 4% of group medians (93% vs. 97% in legend of Figure 1 of the paper) and had no measurable physiologic effect. Is a 2% offset (92% vs. 94%) sufficient or desirable?

Perhaps looking at the data another way may be helpful. Both STOP-ROP

(Figure 4) and BOOST (Figure 1) presented smoothed frequency distributions that showed not only clear offsets in curves, but also the modes of the two curves occurring within the target ranges. A similar set of curves using the current SUPPORT data might reassure us and the DSMB that good separation has been attained. (Or it might alarm us. I'm worried that this will be the case, as the median value for the 85-89% group falls outside the target range.) I've tried to estimate such a curve for the SUPPORT data, but couldn't do it without point-by-point values.

3. The approach of tightening the compliance to targets is obviously the way to proceed forward. The proposed methods sound fine. I'd be more comfortable if there some plan to reassess compliance relatively shortly with another analysis. A couple of suggestions that may help with compliance, both of which fall solidly into other people's baliwicks:

a. The histograms used in STOP-ROP were very powerful images that clearly and simply showed degree of compliance with targets. I couldn't find anyone who remembered specifically, but I think the nurses in our unit did not use them during STOP-ROP. I do think, however, that they would be very useful tools for the nurses to have, as you have suggested.

b. There was considerable inter-center variability in the data you sent. Benchmarking with the most successful centers might be useful.

Since I'm not sure Dale will be voting for our center, I'll cast a vote. If Dale votes, I consider myself over-ruled.

I would favor sending on the response to the DSMB, provided it included some more specific comparison to what other studies of differing saturation targets have been able to achieve. If we have been unable to get the sort of separation achieved by others, the modifications to improve compliance will be even more important. I would also favor proposing a repeat evaluation after the next N (choose your favorite N) subjects to assess any improvement in compliance.

Neil, thanks for the incredible amount of work you and the folks at RTI have done in a very short time.

Carl

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carl_dangio@urmc.rochester.edu

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-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 30, 2005 11:23 AM
To: alaptook@WIHRI.org; Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Phelps, Dale; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle

Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@utsouthwestern.edu
Cc: D'Angio, Carl; Laroia, Nirupama; vanmeurs@stanford.edu; Avroy A. Fanaroff; reverett@med.miami.edu; kurt.schibler@cchmc.org; ambal@uab.edu; Morris, Brenda H; Michael Cotten; Wade Rich; Gantz, Marie; Petrie, Carolyn
Subject: Response to DSMC Steering Nov 30 05

HI,
Attached is the final response to the DSMC as discussed on the phone this morning. Please review this and let me know by tomorrow (December 1) evening if this is acceptable to you and your site.
A special thanks to Neil and RTI (Marie and Abhik) for all the time and effort that has been put into this project!!
Rose
<<Response to DSMC Steering Nov 30 05.doc>>

From: Duara, Shahnaz
To: Neil Finer
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Response to DSMC Steering Nov 30 05.doc
Date: Wednesday, November 30, 2005 4:23:13 PM
Attachments: Response to DSMC Steering Nov 30 05.doc

A few clarifications - nice work!

Shahnaz
<<Response to DSMC Steering Nov 30 05.doc>>

In response to the comments and concerns of the DSMC, the SUPPORT committee held a conference call Monday Nov 28th at 10:00 to 1130AM to prepare a response.

- The DSMC made the following 2 comments in their letter regarding the SUPPORT trial. This was generated after they reviewed the oximeter data, which was corrected back to actual SpO2 values from the altered values displayed at the bedside:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

We have responded to each of these concerns and our responses are detailed below

Response to Issue Number 1

We appreciate the concern expressed by the DSMC regarding a potential safety issue secondary to durations of SpO2 values > 95%. To date there are no prospective data which define the SpO2s experienced by the ELBW infant from birth as part of usual clinical care. Because no published studies have evaluated the effects of different target SpO2 ranges on important outcomes, this was one of the principle reasons for the design and conduct of the SUPPORT trial. A number of studies have evaluated different alarm limits, but have not reported the actual durations of SpO2 in the various ranges. Nghiem et al in a PAS abstract this year reported that nurses caring for ELBW infants believe that an acceptable oxygen saturation range should include higher upper limits than specified by current policy (Nghiem et al, Nursing Opinions and Practices of Oxygenation in Prematures: The NOPOP Study PAS #3415, 2005). The study by Hagadorn reported as a late breaker at the PAS this year (Hagadorn et al, Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation. PAS 2005, Attached) did report on the experience of monitoring the actual SpO2 for 72 hours in the first 4 weeks of life in 72 ELBW infants. They reported that the "lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for a median of 70 hours (25th-75th percentiles 67-71 hr) during each week. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25th-75th percentiles 91-97%; range of study center medians 91-96%). Centers ranged between 16-71% compliance with their individual intended SpO2 range. Most noncompliance was above intended range." In comparing the data evaluated to date by the DSMC, it is of interest that the mean SpO2 in the 2.Oximeter arms is 90% and 92%, with

medians of 92% and 94%, all of which are below that reported by Hagadorn et al (median=95). The 2 other relevant trials, STOP-ROP and BOOST, both enrolled infants at about 32 weeks PCA, and maintained 2 levels of SpO2, 89% to 94% and 91-94% versus 95% to 98% and 96% to 99%, by administration of oxygen. These studies achieved reasonable separation, but did demonstrate substantial overlap of the intended ranges. It is important to note that these studies were testing two ranges both of which were higher than the lower range of the SUPPORT trial (85% to 89%) and were treating infants who, for the most part, had recovered from their acute disease. In the BOOST trial 70% of the enrolled infants were < 28 weeks of age at birth (all of SUPPORT is < 28 weeks), 32 weeks postmenstrual age (PMA), and required oxygen at enrollment (Askie et al, New England Journal of Medicine. 2003; 349(10):959-967). The STOP-ROP trial enrolled infants with pre-threshold ROP at a PMA of 35.4 + 2.5 weeks of age (Phelps et al, Pediatrics. 2000; 105(2):295-310). These trials then gave the higher SpO2 range infants additional oxygen to increase their SpO2 to the desired range. STOP-ROP reported that the infants in the high range had an SpO2 > 95% for > 97% of the monitored time. These studies found an overall increase in pulmonary morbidity in the higher SpO2 range infants.

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The oximetry algorithm that was designed for the SUPPORT trial is such that re-conversion of the altered oximeter values does not result in a discrete SpO2 number for every displayed value. SpO2 values, of 93%, 94% 95% and 96% will all be reconverted to a single value in one arm, while 84%, 85%, 86% and 87% will be reconverted to a single value in the other arm. This is a result of having the displayed values return to non-skewed SpO2 values at < 84% and > 96%, a safety design felt to be important by all involved in this trial (See Attached file USCD1). Thus the percentages reported to the DSMC for some of the ranges that include these values were not an accurate representation of the true values. However all values > 96% and < 84% are actual and do not require any conversion.

Percent of time of spent at SpO2 < 84% and > 96%
(RTI, Nov 29, 2005, 14:00 Hrs)

Range	High target (91-95)	Low target (85-89)
< 84%	8.51	16.62
> 96%	22.69	13.60

In the current SUPPORT study, an initial analyses utilizing only unaltered SpO2 values as shown above , ie those below 84% and above 96% have shown that one arm had an SpO2 > 96% for 13.6% versus 22.69% of the time for the comparison arm, and the durations of an SpO2 < 84% was also different at

16.62% versus 8.51%. The previously reported value of 36% duration of an SpO2 > 95% for one group represented an artifact of the conversion algorithm as described above. The values for SpO2s > 96% using unaltered data suggests that the SUPPORT trial to date has, if anything, reduced the duration of hyperoxia.

In addition, using these values which represent actual SpO2 values, we can state that the infants in this trial are spending approximately 70% of the time with a true SpO2 value between 84% and 96%. We believe that this is information is very encouraging, and suggests that if we are able to further improve adherence to the target ranges that we will achieve an adequate separation between the groups.

As part of the SUPPORT trial, we collect information about inhaled oxygen concentration 3 times a day for the first 14 days and daily thereafter. We believe that a more frequent documentation of inhaled oxygen will allow us to determine the actual duration of oxygen exposure. At the present an infant is considered to be receiving supplemental oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized as receiving supplemental oxygen for significant periods when they are actually in room air. This would result in durations of SpO2 greater than 95% that were felt to be modifiable and reported as such when in fact there is no effective treatment for such elevated SpO2s. In addition, we do not know if such SpO2s on room air are associated with any morbidity. From the SUPPORT study data analyses to date we know that infants in room air have SpO2s > 95% for 46% to 69% of the time.

In view of this design, we would suggest that all future analyses evaluate the ranges of <84% and >96% as those ranges that are considered to be low and high.

We believe that the SUPPORT trial will actually define the periods of time that ELBW infants spend with different ranges of SpO2, and that it is essential to collect this information. In addition, as our findings indicate a lower true percent of the time at SpO2 values >95%, and lower median SpO2 values than has previously been reported, we are in fact, reducing the time with high SpO2 values compared to usual care. The SUPPORT trial carefully evaluates risks, and we will be evaluating group differences for all important short and long term outcomes.

The SUPPORT trial methodology actively encourages all caretakers to keep SpO2 < 96% by having alarm limits set at 85% to 95%. These limits were utilized because it was felt that these represented current practice. The oximetry algorithms were designed to keep infants in the narrower target range of 88% to 92% with the realization that setting alarm limits at these values would severely increase the frequency of the alarms sounding. Nevertheless, our results to date suggest that we have decreased the expected percent of time > 95%, and in one group the value of 14% may be as low as is achievable in an actual clinical environment.

We believe that the SUPPORT study will define the durations of high and low SpO2 and will be able to determine if there is a threshold duration of either value that is associated with altered outcomes, and for this reason alone, the

SUPPORT trial will be very valuable. All of the procedures outlined below in response to your second concern will also allow us to further increase the percentage of time that the infants are in the maximally altered SpO2 ranges which we believe will further increase separation of these groups.

Response to Issue Number 2

There is concern that we have not achieved adequate separation by the current oximeters and study personnel. Reviewing the newest analyses available as described above, there are differences in the durations of low and high SpO2s between the 2 oximeter groups. In addition, a careful analysis of the most recent converted values demonstrates that the cumulative time spent with an SpO2 of 90% or less is 24.3% versus 43%, for the 2 oximeter groups, supporting the ability of the altered oximeters to produce differential SpO2 exposures. We do acknowledge that it would desirable to increase the percentage of time in the narrower target range and towards this end would propose the following changes to SUPPORT:

1. We will require documentation that the alarm limits are set and functional as per protocol every 4-6 hours. We have found that in some units the high alarms are being defeated, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned to the respiratory therapists, and this procedure is already being done in many NRN units.

2. We will immediately initiate a change in our data collection for FiO2. We will change the data form to indicate that the infant was either in oxygen for the entire 24 hours, and if not, will check off the actual hours of oxygen exposure, and we will continue with this from of data collection for the entire time that the infant is receiving oxygen. In the current protocol we collect such information 3 times a day for the first 14 days only and then daily thereafter. We believe that more frequent documentation will allow us to determine the actual time that an infant is in room air. At the present the infant is considered in oxygen if he/she requires oxygen for greater than intermittent use. This results in infants being categorized in oxygen for significant periods when they are in room air. While in room air, we cannot manipulate the SpO2, and thus knowledge of the true time in oxygen will produce a more accurate representation of oximetry results that are subject to care interventions.

Comment [d1]: "form"

Comment [d2]: add "and extended"

3. We will initiate further training and in-service at all the sites to stress the importance of keeping the SpO2 alarm functional and at the limits of 85% and 95%. In the past these were guidelines, and we will now change the study manual and protocol to indicate these limits are now set by protocol and that violations will be documented. We will encourage all caretakers to aim for an SpO2 value of 90% and make every effort to educate caretakers to make smaller

adjustments in FiO2 and ensure that the infant is maintained between the 87% to 93%, the range with the maximal separation of the study oximeters. We will further facilitate the use of the 2 hour and 12 hour histograms showing the infants' actual ranges to provide feedback to the caretakers regarding the percentage of time in the target ranges.

4. We will develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation. We would hope that such changes – ie increasing the FiO2 in steps of 5% as opposed to much larger increases will decrease the resultant overshoots creating the high SpO2 values. This will be included in the revised manual of operations.

5. We will place bedside cards to indicate the target range.

6. We will initiate compliance monitoring visits coordinated by RTI to visit random sites. These visits had been planned, but had not yet been initiated. The teams will consist of a member of RTI and a study coordinator, and they will review the adherence to the protocol and any other relevant issues.

We thank the DSMC for their thoughtful concerns. We trust that our plans to move forward with the SUPPORT trial are acceptable to the DSMC. We are anxious to initiate the above changes, seek IRB approvals and re-activate this trial.

From: Michele Walsh
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Response to DSMC Steering Nov 30 05
Date: Wednesday, November 30, 2005 1:34:04 PM
Attachments: Response to DSMC Steering Nov 30 05MW comment.doc

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Thanks for this excellent work Neil. I spent some time making editorial changes that I believe will facilitate the DSMCs review of this comprehensive and complex document.
(I guess I am still in book editor mode!) Hope this helps.
Michele
----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
To: <alaptook@WIHRI.org>; "Abhik Das" <adas@rti.org>; "Brenda Poindexter" <bpoindex@iupui.edu>; "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>; "Charles Rosenfeld" <crosen@mednet.swmed.edu>; "Dale Phelps" <dale_phelps@urmc.rochester.edu>; "Ed Donovan" <edward.donovan@cchmc.org>; "Ehrenkranz Richard (E-mail)" <richard.ehrenkranz@yale.edu>; "Jobe Alan (E-mail)" <Jobea0@chmcc.org>; "Lemons Jim (E-mail)" <jlemons@iupui.edu>; "Michael O'Shea" <moshea@wfubmc.edu>; "Michelle Walsh" <mcw3@po.cwru.edu>; "Neil Finer" <nfiner@ucsd.edu>; "Oh William (E-mail)" <william_oh@brown.edu>; "Poole Kenneth (E-mail)" <poo@rti.org>; "Ronald GOldberg" <goldb008@mc.duke.edu>; "Shahnaz Duara" <sduara@miami.edu>; "Shankaran Seetha (E-mail)" <s_shankaran@wayne.edu>; "Stevenson David (E-mail)" <dstevenson@stanford.edu>; "Stoll Barbara (E-mail)" <barbara_stoll@oz.ped.emory.edu>; "Tyson Jon (E-mail)" <Jon.E.Tyson@uth.tmc.edu>; <walid.salhab@utsouthwestern.edu>
Cc: "D'Angio, Carl" <Carl_Dangio@URMC.Rochester.edu>; "Laroia, Nirupama" <Nirupama_Laroia@URMC.Rochester.edu>; <vanmeurs@stanford.edu>; "Avroy A. Fanaroff" <aaf2@case.edu>; <reverett@med.miami.edu>; <kurt.schibler@cchmc.org>; <ambal@uab.edu>; "Morris, Brenda H" <Brenda.H.Morris@uth.tmc.edu>; "Michael Cotten" <cotte010@mc.duke.edu>; "Wade Rich" <wrich@ucsd.edu>; "Gantz, Marie" <mgantz@rti.org>; "Petrie, Carolyn" <petrie@rti.org>
Sent: Wednesday, November 30, 2005 11:22 AM
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3. Impact of SUPPORT oximeters algorithm on sat values:

———The oximetry algorithm that was designed for the SUPPORT trial is such that re-conversion of the altered oximeter values does not result in a discrete SpO2 number for every displayed value. SpO2 values, of 93%, 94% 95% and 96% will all be reconverted to a single value in one arm, while 84%, 85%, 86% and 87% will be reconverted to a single value in the other arm. This is a result of having the displayed values return to non-skewed SpO2 values at < 84% and > 96%, a safety design felt to be important by all involved in this trial (See Attached file USCD1). Thus the percentages reported to the DSMC for some of the ranges that include these values were not an accurate representation of the true values. However all values > 96% and < 84% are actual and do not require any conversion.

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< 84%	8.51	16.62
> 96%	22.69	13.60

In the current SUPPORT study, an initial analyseis utilizing only unaltered SpO2 values, ~~as shown above , ie~~ those below 84% and above 96%, have shown that one arm had an SpO2 > 96% for 13.6% versus 22.69% of the time for the comparison arm, and the durations of an SpO2 < 84% was also different at 16.62% versus 8.51%. The previously reported value of 36% duration of an SpO2 > 95% for one group represented an artifact of the conversion algorithm as described above. **The values for SpO2s > 96% using ~~unaltered~~ uncorrected data suggests that the SUPPORT trial to date has, if anything, reduced the duration of hyperoxia~~.~~. compared to that experienced by comparable neonates outside the trial,**

In addition, analyses using ~~these values which represent~~ only actual SpO2 values, ~~we can state that the~~demonstrate that infants in this trial are spending approximately 70% of the time with a true SpO2 value between 84% and 96%. We believe that this is information is very encouraging, and suggests that if we are able to further improve adherence to the target ranges that we will achieve an adequate separation between the groups.

4. Impact of inclusion of data from periods in room air on saturation distributions:

As part of the SUPPORT trial, we collect information about inhaled oxygen concentration 3 times a day for the first 14 days and daily thereafter. We believe that a more frequent documentation of inhaled oxygen will allow us to determine the actual duration of oxygen exposure. At the present an infant is considered to be receiving supplemental oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized as receiving supplemental oxygen for significant periods when they are actually in room air. This would result in durations of SpO2 greater than 95% that were felt to be modifiable and reported as such when in fact there is no effective treatment for such elevated SpO2s. In addition, we do not know if such SpO2s on room air are associated with any morbidity. From the SUPPORT study data analyses to date we know that infants in room air have SpO2s > 95% for 46% to 69% of the time.

In view of this design, we would suggest that all future analyses for the DSMC evaluate the saturation ranges of <84% and >96% in children on oxygen therapy as those ranges that are outside the target range. ~~considered to be low and high.~~

We believe that the SUPPORT trial will actually define the periods of time that ELBW infants spend with different ranges of SpO2, and that it is essential to collect this information. In addition, as our findings indicate a lower true percent of the time at SpO2 values >95%, and lower median SpO2 values than has previously been reported, we are in fact, reducing the time with high SpO2 values compared to usual care. The SUPPORT trial carefully evaluates risks, and we will be evaluating group differences for all important short and long term outcomes.

The SUPPORT trial methodology actively encourages all caretakers to keep SpO2 < 96% by having alarm limits set at 85% to 95%. These limits were utilized because it was felt that these represented current practice. The oximetry algorithms were designed to keep infants in the narrower target range of 88% to 92% with the realization that setting alarm limits at these values would severely

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increase the frequency of the alarms sounding. Nevertheless, our results to date suggest that we have decreased the expected percent of time > 95%, and in one group the value of 14% may be as low as is achievable in an actual clinical environment.

We believe that the SUPPORT study will define the durations of high and low SpO2 and will be able to determine if there is a threshold duration of either value that is associated with altered outcomes, and for this reason alone, the SUPPORT trial will be very valuable. All of the procedures outlined below in response to your second concern will also allow us to further increase the percentage of time that the infants are in the maximally altered SpO2 ranges which we believe will further increase separation of these groups.

Response to Issue Number 2

There is concern that we have not achieved adequate separation by the current oximeters and study personnel.

1. As described above, ~~Reviewing~~ the newest analyses ~~available as described above, there are~~ show differences in the durations of low and high SpO2s between the 2 oximeter groups. ~~In addition, A~~a careful analysis of the most recent converted values demonstrates that the cumulative time spent with an SpO2 of 90% or less is 24.3% versus 43%, for the 2 oximeter groups, supporting the ability of the altered oximeters to produce differential SpO2 exposures.

2. We do acknowledge that it would desirable to increase the percentage of time in the narrower target range and towards this end would propose the following changes to SUPPORT:

A~~1~~. We will require **documentation that the alarm limits are set and functional as per protocol every 4-6 hours**. We have found that in some units the high alarms are being defeated, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned to the respiratory therapists, and this procedure is already being done in ~~many~~ some NRN units.

B~~2~~. We will immediately initiate a **change in our data collection for FiO2 to ensure that DSMC reports more accurately reflect saturations measured while on oxygen therapy and exclude saturations of infants in room air**. We will change the data form to indicate that the infant was either in oxygen for the entire 24 hours, and if not, will check off the actual hours of oxygen exposure, and we will continue with this from of data collection for the entire time that the infant is receiving oxygen. In the current protocol we collect such information 3 times a day for the first 14 days only and then daily thereafter. We believe that more frequent documentation will allow us to determine the actual time that an infant is in room air. At the present the infant is considered in oxygen if he/she requires oxygen for greater than intermittent use. This results in infants being

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categorized in oxygen for significant periods when they are in room air. While in room air, we cannot manipulate the SpO2, and thus knowledge of the true time in oxygen will produce a more accurate representation of oximetry results that are subject to care interventions.

3C. We will initiate **further training and in-service at all the sites to stress the importance of keeping the SpO2 alarm functional and at the limits of 85% and 95%.** In the past these were guidelines, and we will now change the study manual and protocol to indicate these limits are now set by protocol and that violations will be documented. We will encourage all caretakers to aim for an SpO2 value of 90% and make every effort to educate caretakers to make smaller adjustments in FiO2 and ensure that the infant is maintained between the 87% to 93%, the range with the maximal separation of the study oximeters. We will further facilitate the use of the 2 hour and 12 hour histograms showing the infants' actual ranges to provide feedback to the caretakers regarding the percentage of time in the target ranges.

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D.4. We will **develop guidelines for managing desaturations such that the increase in oxygen is proportional to the severity of the desaturation**. More modulated increases in oxygen during these desaturation events will minimize overshoot and the potential of high SpO2 values. ~~We would hope that such changes – ie increasing the FiO2 in steps of 5% as opposed to much larger increases will decrease the resultant overshoots creating the high SpO2 values~~. This will be included in the revised manual of operations.

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5. **We will place bedside cards to indicate the target range**.

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6. We will **initiate compliance monitoring visits coordinated by RTI** to visit random sites. These visits had been planned, but had not yet been initiated. The teams will consist of a member of RTI and a study coordinator, and they will review the adherence to the protocol and any other relevant issues.

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We thank the DSMC for their thoughtful concerns. We trust that our plans to move forward with the SUPPORT trial are acceptable to the DSMC. We are anxious to initiate the above changes, seek IRB approvals and re-activate this trial.

From: Spong, Catherine (NIH/NICHD)
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: DSMC
Date: Wednesday, November 30, 2005 11:51:19 AM

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also you need a rec from the chair - however the chair wants to do it (by email, phone calls individually or conf call etc) is fine - doesnt matter....their call

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From: Higgins, Rosemary (NIH/NICHD)
Sent: Wed 11/30/2005 11:07 AM
To: Spong, Catherine (NIH/NICHD)
Subject: DSMC

Cathy
The PI's of the SUPPORT trial have developed a written response which includes additional data analyses that are likely to support resumption of the trial. I had asked RTI to get the DSMC together on a phone call – it is becoming a problem with the upcoming holidays – I am under the impression that we need approval from each and every member, correct? Let me know
Thanks
Rose

Rosemary D. Higgins, M.D.
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Spong, Catherine (NIH/NICHD)
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: DSMC
Date: Wednesday, November 30, 2005 11:08:23 AM

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this can be done by email if desired

From: Higgins, Rosemary (NIH/NICHD)
Sent: Wed 11/30/2005 11:07 AM
To: Spong, Catherine (NIH/NICHD)
Subject: DSMC

Cathy
The PI's of the SUPPORT trial have developed a written response which includes additional data analyses that are (b) (5) [redacted] I had asked RTI to get the DSMC together on a phone call – it is becoming a problem with the upcoming holidays – I am under the impression that we need approval from each and every member, correct? Let me know
Thanks
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From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD) [E]
Cc:	nfiner@ucsd.edu; "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"; Maynard.Rasmussen@sharp.com
Date:	Wednesday, November 30, 2005 11:08:01 AM
Attachments:	Askie NEJM.pdf Response to DSMC Steering Nov 30 05.doc 20040226AVIOxLateBreakerDraft.doc ucsd1.doc STOP-ROP.pdf

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Hi Rose
Here is the current version with the changes from the call. I re-added Michele's data as it is current and reflects NRN practice. Your call if you feel this part should stay.
I have attached all the relevant material that we would want to send to the DSMC.
I will relook at the RTI data after the run is complete. If this results in major changes I will discuss with you.
Many thanks
Neil

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oxygen-Saturation Targets and Outcomes in Extremely Preterm Infants

Lisa Maree Askie, Ph.D., M.P.H., David John Henderson-Smart, Ph.D., M.B., B.S., Les Irwig, Ph.D., M.B., B.Ch., and Judy Margaret Simpson, Ph.D.

ABSTRACT

BACKGROUND

Physiological studies have shown that chronic hypoxemia may occur in preterm infants who require supplemental oxygen for extended periods and that this hypoxemia may contribute to poor growth and development. Anecdotal reports and uncontrolled observational studies have suggested that a higher oxygen-saturation range may be beneficial in terms of growth and development.

METHODS

We conducted a multicenter, double-blind, randomized, controlled trial involving 358 infants born at less than 30 weeks of gestation who remained dependent on supplemental oxygen at 32 weeks of postmenstrual age. They were randomly assigned to a target functional oxygen-saturation range of either 91 to 94 percent (standard-saturation group) or 95 to 98 percent (high-saturation group); this target was maintained for the duration of supplemental-oxygen therapy. The primary outcomes were growth and neurodevelopmental measures at a corrected age of 12 months.

RESULTS

There were no significant differences between the groups in weight, length, or head circumference at a corrected age of 12 months. The frequency of major developmental abnormalities also did not differ significantly between the standard-saturation group and the high-saturation group (24 percent and 23 percent, respectively, P=0.85). There were six deaths due to pulmonary causes in the high-saturation group and one such death in the standard-saturation group (P=0.12). The high-saturation group received oxygen for a longer period after randomization (median, 40 days vs. 18 days; P<0.001) and had a significantly higher rate of dependence on supplemental oxygen at 36 weeks of postmenstrual age and a significantly higher frequency of home-based oxygen therapy.

CONCLUSIONS

Targeting a higher oxygen-saturation range in extremely preterm infants who were dependent on supplemental oxygen conferred no significant benefit with respect to growth and development and resulted in an increased burden on health services.

From the Centre for Perinatal Health Services Research (L.M.A., D.J.H.-S.) and the School of Public Health (L.I., J.M.S.), University of Sydney, Sydney, Australia. Address reprint requests to Dr. Askie at the Centre for Perinatal Health Services Research, Queen Elizabeth II Research Institute, Bldg. DO2, University of Sydney, Sydney NSW 2006, Australia, or at lisa.askie@perinatal.usyd.edu.au.

N Engl J Med 2003;349:959-67.

Improved survival of extremely preterm infants[1] has been associated with an increase in the incidence of chronic lung disease of infancy,[2] currently defined by a continued dependence on supplemental oxygen at 36 weeks of postmenstrual age.[3,4] This increased incidence has become a major clinical challenge, since chronic lung disease has serious health consequences, including poor growth,[5,6] neurologic impairment,[5,7] and pulmonary sequelae.[5,8] These and other factors may account for the higher reported health care costs for these infants than for infants who do not have chronic lung disease.[9]

Physiological studies have shown that infants with chronic lung disease (also known as bronchopulmonary dysplasia) have higher rates of oxygen consumption than infants without chronic lung disease,[10] as well as lower base-line oxygen-saturation levels, leading to more frequent episodes of desaturation.[11,12] In addition, observational studies have suggested that preterm infants who receive greater levels of oxygen supplementation, with either a longer duration of treatment or a higher target blood oxygen level, have improvements in sleep patterns,[13,14] growth, and neurodevelopmental outcomes.[15,16] Because of the uncontrolled nature of the studies, it is not known whether these associations are causal.

A policy of routine targeting of higher oxygen-saturation levels in preterm infants might result in some substantial burdens for the health care system and for parents, by increasing the duration of oxygen therapy in the hospital and the frequency of the need for home-based oxygen therapy. Despite some potential costs and the lack of evidence of long-term benefits, such policies are increasingly being implemented in clinical practice.[17,18] Data from randomized, controlled trials are lacking,[19,20] and the question of the most appropriate oxygen-saturation levels for preterm infants who require supplemental oxygen remains controversial.[21-23]

We conducted the randomized, multicenter Benefits of Oxygen Saturation Targeting (BOOST) trial to determine whether maintaining the oxygen saturation at a level higher than the standard range in extremely preterm infants with a long-term dependence on supplemental oxygen improves growth and neurodevelopmental outcomes. Secondary aims were to determine whether the higher oxygen-saturation levels had other beneficial or adverse physical or psychosocial effects on infants or parents.

METHODS

CRITERIA FOR ELIGIBILITY

Infants born at less than 30 weeks of gestational age (determined on the basis of the first day of the mother's last menstrual period, prenatal ultrasonography, or both or, if these data were not available, postnatal clinical assessment) who remained dependent on supplemental oxygen (delivered by any method and at any level) at 32 weeks of postmenstrual age were eligible for enrollment. Dependence on supplemental oxygen at 32 weeks of postmenstrual age, rather than 36 weeks, was used as a criterion for inclusion because it was current clinical practice to choose between the standard target range for oxygen saturation and a higher target range at this point in the infant's life. Criteria for exclusion before randomization included major congenital abnormalities, major surgery or a severe intracranial disorder diagnosed before 32 weeks of postmenstrual age, and a multiple birth in which three or more infants were eligible. The protocol allowed for infants from multiple gestations resulting in two eligible infants to be assigned to the same treatment.

The institutional ethics committees of the eight tertiary perinatal enrollment centers participating in the study approved the trial protocol, and written, informed consent was obtained from a parent or guardian of each eligible infant. Infants were enrolled between September 1996 and September 2000.

INTERVENTION AND BLINDING

Infants were randomly assigned to a target oxygen-saturation range of either 91 to 94 percent (standard-saturation group) or 95 to 98 percent (high-saturation group), as measured with a pulse oximeter (model N-3000, Nellcor) whose algorithm assesses functional oxygen saturation.[24] Randomization was stratified with the use of a dynamic balancing method[25] to ensure a balance of treatment-group assignments within each stratum defined according to hospital, singleton or multiple birth, and gestational age (22 to 27 weeks or 28 to 29 weeks). Central telephone randomization ensured concealment of the treatment-group assignments.

To make sure that the treatment-group assignments were not revealed, the infants who underwent randomization were assigned a specific study oximeter, which after the calculation of the infant's

oxygen-saturation level in the usual manner, was adjusted to display a value 2 percent higher than the actual saturation in infants in the standard-saturation group or 2 percent lower than the actual saturation in infants in the high-saturation group. Staff members and parents were then asked to target the range of 93 to 96 percent for the infant's oxygen saturation, so that they remained unaware of the actual ranges being targeted. Caregivers were aware that they were using adjusted oximeters and that they were participating in a trial, but they were not aware of the offset level of the individual oximeter. Double-blind targeting of the assigned saturation range was maintained for the duration of the infant's oxygen therapy either in the hospital (in both the enrollment center and other hospitals if necessary) or at home.

Dependence on supplemental oxygen was defined by the continuing need for oxygen therapy in order to maintain the double-blind target oxygen-saturation range of 93 to 96 percent, as measured by the assigned study oximeter. The frequency of monitoring of the saturation (continuous or intermittent), the settings for limits that were to trigger alarms, and the criteria for titrating the amount of ambient oxygen delivered or for ceasing delivery were determined by the attending clinicians and were not specified by the trial protocol.

ADHERENCE TO THE PROTOCOL

Compliance with the double-blind target oxygen-saturation range of 93 to 96 percent was assessed with the use of twice-weekly downloading of each infant's oxygen-saturation data, and a report on the distribution of the double-blind saturation levels was placed in the case notes. Clinicians and parents were allowed to violate the protocol either temporarily or permanently if they believed that the infant's condition warranted high-saturation oxygen therapy — for instance, because of serious intercurrent illness, as treatment for prethreshold retinopathy of prematurity, or during surgery.

PRIMARY OUTCOMES

The primary outcomes assessed at a corrected age of one year (the chronologic age plus the number of weeks of prematurity) included growth, in terms of the mean weight, the mean length, the mean head circumference, and the proportion of infants with a weight below the 10th percentile,[26] and the presence of a major developmental abnormality, defined as blindness, cerebral palsy, or a score on the revised Griffiths Mental Developmental Scales that was more than 2 SD below the mean (general quotient, <77).[27] Blindness was defined as a visual acuity in both eyes of less than 6/60.[28] Cerebral palsy was diagnosed if the child had nonprogressive motor impairment characterized by abnormal muscle tone and a decreased range or decreased control of movements, accompanied by neurologic signs.[29]

SECONDARY OUTCOMES

The secondary outcomes included the effect of the treatment-group assignment on the duration of oxygen therapy, the duration of assisted ventilation and of the hospital stay, and the frequency of home-based oxygen therapy. Parental stress and parent–infant interaction were assessed by means of validated scales (the Edinburgh Postnatal Depression Scale,[30] the Infant Temperament Questionnaire,[31] the Toddler Temperament Scale,[32] the Parenting Stress Index, Short Form,[33] and the Impact-on-Family Scale[34]). Retinopathy of prematurity was assessed by routine ophthalmic examinations at two-week intervals from enrollment until the resolution of retinopathy, with grading according to the International Classification of Retinopathy of Prematurity.[35] Reports by the parents on the use of health services and rehospitalizations during the first year of life were obtained through quarterly telephone contact by the research nurses, and rehospitalizations were confirmed through a review of the medical records. Causes of death were classified according to the codes of the *International Classification of Diseases, Ninth Revision*,[36] and confirmed on the basis of the hospital discharge summary, a postmortem examination report, a coroner's report, or a death certificate.

STATISTICAL ANALYSIS

All data analyses were performed according to the intention-to-treat principle. For continuous data, the treatment effect was calculated by subtracting the value for the standard-saturation group from the value for the high-saturation group, with results for normally distributed data presented as means ±SD and results for non–normally distributed data presented as medians with interquartile ranges. Differences between the two groups were assessed with the use of Student's t-test or the Mann–Whitney U test and are expressed as mean or median differences, respectively, with 95 percent confidence in-

tervals. For categorical data, the chi-square test was used, and the treatment effects are expressed as relative risks in the high-saturation group as compared with the standard-saturation group, with 95 percent confidence intervals. For analyses involving small numbers of events, Fisher's exact test was used, and exact confidence intervals were calculated for odds ratios, as approximate relative risks. All P values are two-sided and have not been adjusted for multiple testing or for correlation between the outcomes in siblings, since only 25 pairs of siblings were included (a total of 50 infants), representing 14 percent of the infants, and they were distributed approximately equally between the two groups.

The required sample size was calculated to ensure detection of clinically important effects on the primary outcomes: a reduction from the base-line estimate of 47 percent to 30 percent in the proportion of infants with a weight below the 10th percentile at a corrected age of 12 months, and a reduction in the frequency of major developmental abnormalities from 23 percent to 12 percent.[37] To achieve 80 percent power with a two-sided alpha level of 0.05 and a 1:1 ratio of infants in the two groups, approximately 150 infants were required in each group.

Table 1. Base-Line Characteristics of the Infants and Mothers.*

Characteristic	Standard-Saturation Group (N=178)	High-Saturation Group (N=180)
Birth weight — g	918±229	916±231
Gestational age at birth — wk	26.6±1.7	26.5±1.6
<28 Wk of gestation at birth — no. (%)	124 (70)	132 (73)
Male sex — no. (%)	92 (52)	97 (54)
Singleton birth — no. (%)	133 (75)	129 (72)
Born in tertiary care center — no. (%)	163 (92)	172 (96)
Surfactant treatment — no. (%)	138 (78)	137 (76)
Patent ductus arteriosus — no. (%)	94 (53)	91 (51)
Total duration of parenteral nutrition — days		
Median	13.5	13.0
Interquartile range	9.0–20.0	9.0–20.0
Antenatal corticosteroids — no. (%)	148 (83)	149 (83)
Score on the Edinburgh Postnatal Depression Scale†	10.7±5.7	10.0±5.3
Maternal educational level >high school — no. (%)	60 (34)	64 (36)
Maternal occupation score‡	4.5±1.4	4.6±1.3

* Plus–minus values are means ±SD.
† Scores range from 0 to 30, with higher scores indicating greater severity of depressive symptoms.[30]
‡ Data are the scores on Daniel's occupation scale[38]; scores range from 1 to 7, with lower scores indicating higher occupational prestige.

An independent safety monitoring committee, comprising a pediatric ophthalmologist, a neonatologist, and a pediatric respiratory physician–epidemiologist, all of whom were unaware of the treatment-group assignments, assessed adverse outcomes, including death, at five prespecified time points. The stopping rules were never breached.

RESULTS

PARTICIPANTS

Of the 703 infants who were eligible during the enrollment period, 158 met the criteria for exclusion before randomization. A total of 187 of the remaining 545 eligible infants were not enrolled (consent was not obtained for 122 infants, and the parent or guardian was not approached for 65 infants). There were 333 infants who underwent individual randomization, and an additional 25 eligible multiples were assigned to the same group as their sibling, for a total of 358 individual infants receiving one of the two treatments for whom outcomes were analyzed. A total of 178 infants were assigned to the standard-saturation group (target oxygen saturation, 91 to 94 percent) and 180 to the high-saturation group (target oxygen saturation, 95 to 98 percent). The two groups were well balanced in terms of the base-line characteristics of the infants and the mothers (Table 1). The intervention continued for a median of 17.5 days (interquartile range, 7.0 to 41.0) in the standard-saturation group and 40.0 days (interquartile range, 20.5 to 73.0) in the high-saturation group ($P<0.001$).

ADHERENCE TO THE PROTOCOL

Figure 1 shows the two distributions of the actual saturation levels. The median for each group was within the desired target range. Permitted protocol violations for open targeting of the oxygen saturation occurred relatively infrequently (on 54 occasions), generally for short periods (median, 7 days; interquartile range, 3 to 17), and the occurrences were equally distributed between the two groups.

PRIMARY OUTCOMES

The rate of ascertainment of primary outcomes was 93 percent in the standard-saturation group (165 of 178 infants) and 93 percent in the high-saturation group (168 of 180 infants). The median age at the assessment of the primary outcomes did not differ between the two groups (a corrected age of 12.1 months [interquartile range, 11.8 to 12.7] in the standard-saturation group and a corrected age of

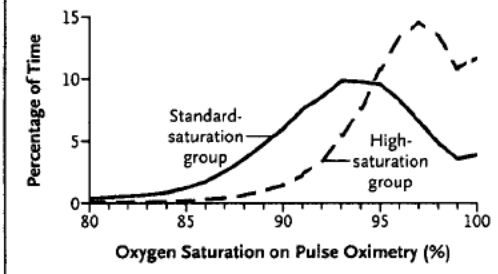

Figure 1. Smoothed Frequency Distribution of Actual Oxygen-Saturation Values on Pulse Oximetry during Oxygen Therapy after Randomization.

The saturation values were sampled every 10 seconds during intermittent downloads performed approximately twice weekly and lasting 8 to 24 hours each. The median oxygen saturation was 93 percent in the standard-saturation group (interquartile range, 90 to 96) and 97 percent in the high-saturation group (interquartile range, 94 to 98).

12.2 months [interquartile range, 11.9 to 12.9] in the high-saturation group).

There were no significant differences between the two groups in the mean weight, length, or head circumference at 38 weeks of postmenstrual age (Table 2). In addition, at a corrected age of 12 months, there were no significant differences in the measurements of weight, length, or head circumference; the proportion of infants who were small for their age; or the proportion of infants with a major developmental abnormality (Table 2). Our data also showed no significant difference between the two groups in the frequency of developmental scores that were more than 1 SD but less than 2 SD below the mean (relative risk associated with the higher oxygen-saturation target, 1.08; 95 percent confidence interval, 0.69 to 1.69; P=0.70). When the primary outcomes were examined in the subgroup of 256 infants born before 28 weeks of gestation, the differences between the two treatment groups remained nonsignificant and were similar

Table 2. Measures of Growth and Development.*

Outcome	Standard-Saturation Group	High-Saturation Group	Mean Difference (95% CI)	Relative Risk or Odds Ratio (95% CI)†	P Value
38 Wk of postmenstrual age					
Weight — g	2345±429	2369±428	24.0 (−66 to 113)		0.60
Length — cm	44.2±3.2	44.2±3.2	0.0 (−0.6 to 0.7)		1.00
Head circumference — cm	33.1±2.2	32.9±1.9	−0.2 (−0.7 to 0.2)		0.26
12 Mo of corrected age					
Weight — kg	9.10±1.5	9.25±1.6	0.15 (−0.2 to 0.5)		0.33
Length — cm	74.0±3.9	74.1±4.1	0.1 (−0.8 to 1.0)		0.77
Head circumference — cm	46.3±2.0	46.3±1.9	0.0 (−0.4 to 0.4)		1.00
Weight below 10th percentile — no./total no. (%)	61/165 (37)	55/168 (33)		0.89 (0.66 to 1.19)	0.42
Length below 10th percentile — no./total no. (%)	42/162 (26)	41/164 (25)		0.96 (0.67 to 1.40)	0.85
Head circumference below 3rd percentile — no./total no. (%)	5/165 (3)	8/165 (5)		1.63 (0.46 to 6.47)	0.57
Major developmental abnormality — no./total no. (%)‡	40/166 (24)	39/168 (23)		0.96 (0.66 to 1.42)	0.85

* Plus–minus values are means ±SD. Denominators are the numbers of infants for whom growth measures or major developmental abnormalities could be assessed at 12 months of corrected age. CI denotes confidence interval.

† The value for a head circumference below the 3rd percentile is an odds ratio; other values are relative risks.

‡ Major developmental abnormalities were blindness, cerebral palsy, or a general quotient on the revised Griffiths Mental Developmental Scales that was more than 2 SD below the mean.

in magnitude to those in the whole cohort (data not shown).

SECONDARY OUTCOMES

The proportion of infants who were still dependent on supplemental oxygen at 36 weeks of postmenstrual age was 46 percent in the standard-saturation group and 64 percent in the high-saturation group (P<0.001) (Table 3). Similarly, the proportion of infants requiring home-based oxygen therapy was significantly lower in the standard-saturation group than in the high-saturation group (17 percent vs. 30 percent, P=0.004) (Table 3). The duration of oxygen supplementation was significantly higher in the high-saturation group: the postmenstrual age at the cessation of oxygen therapy was 35.4 weeks in the standard-saturation group and 37.9 weeks in the high-saturation group (P<0.001) (Table 3). There were no significant differences between the two groups in the median total duration of assisted ven-

Table 3. Rates of Adverse Outcomes among the Infants.*

Outcome	Standard-Saturation Group (N=178)	High-Saturation Group (N=180)	Relative Risk or Odds Ratio (95% CI)†	Median Difference (95% CI)	P Value
Dependence on supplemental oxygen at 36 wk of postmenstrual age — no. (%)	82 (46)	116 (64)	1.40 (1.15 to 1.70)		<0.001
Home-based oxygen therapy — no. (%)	30 (17)	54 (30)	1.78 (1.20 to 2.64)		0.004
Duration of oxygen therapy after randomization — days				17 (12 to 23)	<0.001
Median	17.5	40.0			
Interquartile range	7.0 to 41.0	20.5 to 73.0			
Postmenstrual age at cessation of oxygen therapy — wk				2.3 (1.3 to 3.3)	<0.001
Median	35.4	37.9			
Interquartile range	33.4 to 39.7	35.4 to 45.1			
Duration of assisted ventilation after randomization — days				0 (−4 to 4)	0.95
Median	14.0	14.0			
Interquartile range	7.0 to 28.0	6.0 to 35.0			
Postnatal corticosteroids — no. (%)	89 (50)	104 (58)	1.16 (0.95 to 1.40)		0.14
Diuretics for chronic lung disease — no. (%)	78 (44)	93 (52)	1.18 (0.95 to 1.47)		0.14
Length of hospital stay after randomization — days				2 (−1 to 5)	0.24
Median	50.0	50.0			
Interquartile range	39.0 to 60.0	42.0 to 61.5			
Postmenstrual age at discharge from hospital — wk				0.29 (−0.14 to 0.86)	0.15
Median	39.1	39.1			
Interquartile range	37.4 to 40.4	37.9 to 40.8			
Postmenstrual age at time of fully oral feeding — wk				0.00 (−0.43 to 0.43)	0.91
Median	37.7	37.7			
Interquartile range	36.6 to 39.0	36.4 to 38.9			
Worst retinopathy of prematurity — no. (%)					
<Stage 3	150 (84)	158 (88)	1.04 (0.96 to 1.13)		0.34
Stage 3 or 4	28 (16)	22 (12)	0.78 (0.46 to 1.31)		0.34
Ablative retinal surgery for severe retinopathy of prematurity — no. (%)‡	20 (11)	11 (6)	0.54 (0.27 to 1.10)		0.09
Death (after randomization) — no. (%)	5 (3)	9 (5)	1.82 (0.53 to 7.05)		0.41

* CI denotes confidence interval.
† The value for death is an odds ratio; all other values are relative risks.
‡ Data are for infants who underwent cryotherapy or laser therapy for threshold retinopathy of prematurity, usually stage 3 with dilatation of the posterior retinal vessels (referred to as "plus" disease).

tilation after randomization, the rate of use of postnatal corticosteroids or diuretics, the length of the hospital stay after randomization, the postmenstrual age at discharge, or the time before the infant was able to be fed entirely orally (Table 3).

There were no significant differences between the groups in the rates of retinopathy of prematurity of any stage or in the frequency of the need for ablative retinal surgery (in 20 of 178 infants in the standard-saturation group [11 percent] and 11 of 180 infants in the high-saturation group [6 percent], P=0.09) (Table 3). All the infants who underwent ablative retinal surgery were born before 28 weeks of gestation, and all but one of these infants retained vision in at least one eye. The rate of ablative retinal surgery among infants born before 28 weeks of gestation was 16 percent (20 of 124 infants) in the standard-saturation group and 8 percent (11 of 132 infants) in the high-saturation group (relative risk, 0.52; 95 percent confidence interval, 0.26 to 1.03; P=0.06).

There was no significant difference between the two groups in the number of infants who died: five infants in the standard-saturation group and nine in the high-saturation group (Table 3). Of these deaths, one in the standard-saturation group was due to pulmonary causes, as compared with six in the high-saturation group (P=0.12). The number of infants who were rehospitalized and the number of health service visits per infant during the first year of life did not differ significantly according to the treatment group (Table 4). There were also no significant differences between the two groups in the measures of maternal postnatal depression, infant or toddler temperament, parental stress, or effects on the family (Table 4). Follow-up rates for these tests ranged from 71 to 77 percent.

DISCUSSION

Our double-blind, randomized trial showed no evidence that the targeting of a functional oxygen-saturation range of 95 to 98 percent rather than a range of 91 to 94 percent had a beneficial effect on growth or development in preterm infants with a long-term dependence on supplemental oxygen. The targeting of higher oxygen-saturation levels resulted in a 40 percent increase in the proportion of infants who were still receiving oxygen therapy at 36 weeks of postmenstrual age and a 78 percent increase in the

Table 4. Use of Health Services in the First Year of Life and Psychosocial Measures in Parents and Infants.*

Outcome	Standard-Saturation Group	High-Saturation Group	Relative Risk (95% CI)	Difference between Groups (95% CI)†	P Value
Infant rehospitalized — no./total no. (%)	82/171 (48)	92/170 (54)	1.13 (0.92 to 1.39)		0.34
No. of health service visits/infant				3.8 (−0.8 to 8.5)	0.11
Median	27.5	31.3			
Interquartile range	25.1 to 30.4	27.3 to 34.8			
Scores on psychosocial measures‡					
Edinburgh Postnatal Depression Scale (mother)	5.9±5.1	6.5±4.8		0.6 (−0.6 to 1.8)	0.32
Infant Temperament Scale	2.3±0.7	2.4±0.7		0.1 (0.0 to 0.3)	0.06
Toddler Temperament Scale	3.2±0.6	3.1±0.6		−0.1 (−0.2 to 0.1)	0.59
Parenting Stress Index, Short Form	71.7±20.6	72.9±21.1		1.2 (−3.9 to 6.3)	0.65
Impact-on-Family Scale	40.0±11.0	39.8±11.7		−0.2 (−3.0 to 2.6)	0.89

* Plus–minus values are means ±SD. Scores on the Edinburgh Postnatal Depression Scale[30] range from 0 to 30, with higher scores indicating a greater severity of depressive symptoms. Scores on the Infant Temperament Scale[31] range from 1 to 6, with a mean (±SD) of 2.5±0.64; higher scores indicate a more difficult temperament. Scores on the Toddler Temperament Scale[32] range from 1 to 6, with a mean of 3.46±0.62; higher scores indicate a more difficult temperament. Scores on the Parenting Stress Index, Short Form,[33] range from 32 to 160, with a median of 69 (interquartile range, 61 to 79); higher scores indicate greater parental stress. Scores on the Impact-on-Family Scale[34] range from 19 to 76, with a mean of 46.2±7.6; higher scores indicate increased effects on the family. CI denotes confidence interval.

† The mean difference is shown for scores on psychosocial measures; the median difference is shown for health service visits.

‡ The score on the Infant Temperament Scale was obtained at 4 months of corrected age; scores on the other measures were obtained at 12 months of corrected age.

proportion receiving supplemental oxygen after discharge. Hence, one could expect one additional case of home-based oxygen therapy for every eight infants treated if higher target ranges for the oxygen saturation were used routinely.

The finding that oxygen therapy was required for a longer period in the high-saturation group might simply be explained by the fact that a higher target saturation had to be reached for oxygen therapy to be discontinued. However, a higher target oxygen saturation may also be associated with potential pulmonary toxicity. The unexpected finding of excess deaths from pulmonary causes among infants in the high-saturation group — albeit not statistically significant — accords with the findings of the only other trial in which preterm infants were randomly assigned to different target oxygen-saturation ranges, the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial.[39] That trial showed an increased rate of adverse pulmonary sequelae (although not an increased rate of death due to pulmonary causes) among preterm infants with prethreshold retinopathy of prematurity when a higher oxygen-saturation range was targeted.

Oxygen toxicity, particularly in preterm infants, can inhibit lung healing and contribute to ongoing lung injury.[40] In our trial, infants who were still dependent on supplemental oxygen at 36 weeks of postmenstrual age or before discharge did not routinely have oxygen-saturation data collected after a room-air breathing test, and we do not have information on the proportion of infants in the high-saturation group who would not have required oxygen had their oxygen-saturation target been lower. Thus, the cause of the greater oxygen requirement in the high-saturation group remains uncertain.

Although our trial did not have the statistical power to detect differences in secondary eye-related outcomes, the effect of different target oxygen-saturation ranges on retinopathy of prematurity is of interest, since infants were randomly assigned to the different treatments at 32 weeks of postmenstrual age, before threshold retinopathy of prematurity usually develops. The results of both the STOP-ROP trial and our trial suggest the possibility that the need for ophthalmic intervention may be reduced when a higher oxygen-saturation range is targeted in a subgroup of extremely preterm infants with more severe eye disease. However, the differences between the treatment groups were not significant at the $P<0.05$ level in our subgroup analysis, and this hypothesis requires confirmation in larger studies.

Our trial addressed only the question of the effects of two different target oxygen-saturation ranges in preterm infants who remained dependent on supplemental oxygen after 32 weeks of postmenstrual age. Hence, these results should not be extrapolated to practice recommendations for preterm infants at earlier postmenstrual ages. The question of the most appropriate oxygen-saturation range for preterm infants treated sooner after birth can be answered only in the context of further large, well-designed, randomized trials with good long-term follow-up.[21]

A possible limitation of the study is that the duration of follow-up may not have been sufficiently long to allow us to detect other clinically important outcomes, such as minor disabilities that may become manifest later in childhood. We found no significant difference in the rates of developmental scores that were more than 1 SD but less than 2 SD below the mean — an outcome that may be a surrogate for later minor disability.[41]

The results of this randomized trial contradict observational reports suggesting that there are benefits of the routine targeting of higher oxygen-saturation levels in preterm infants with a long-term dependence on supplemental oxygen.[13-16] We found no evidence of beneficial effects of higher oxygen-saturation levels on growth or neurodevelopmental outcomes in these infants, but we did find an increased burden on health services.

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In response to the comments and concerns of the DSMC, the SUPPORT committee held a conference call Monday Nov 28th at 10:00 to 1130AM to prepare a response.

- The DSMC made the following 2 comments in their letter regarding the SUPPORT trial. This was generated after they reviewed the oximeter data, which was corrected back to actual SpO2 values from the altered values displayed at the bedside:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

We have responded to each of these concerns and our responses are detailed below

Response to Issue Number 1

We appreciate the concern expressed by the DSMC regarding a potential safety issue secondary to durations of SpO2 values > 95%. To date there are no prospective data which define the SpO2s experienced by the ELBW infant from birth as part of usual clinical care. Because no published studies have evaluated the effects of different target SpO2 ranges on important outcomes, this was one of the principle reasons for the design and conduct of the SUPPORT trial. A number of studies have evaluated different alarm limits, but have not reported the actual durations of SpO2 in the various ranges. Nghiem et al in a PAS abstract this year reported that nurses caring for ELBW infants believe that an acceptable oxygen saturation range should include higher upper limits than specified by current policy (Nghiem et al, Nursing Opinions and Practices of Oxygenation in Prematures: The NOPOP Study PAS #3415, 2005). The study by Hagadorn reported as a late breaker at the PAS this year (Hagadorn et al, Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation. PAS 2005, Attached) did report on the experience of monitoring the actual SpO2 for 72 hours in the first 4 weeks of life in 72 ELBW infants. They reported that the "lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for a median of 70 hours (25th-75th percentiles 67-71 hr) during each week. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25th-75th percentiles 91-97%; range of study center medians 91-96%). Centers ranged between 16-71% compliance with their individual intended SpO2 range. Most noncompliance was above intended range." In comparing the data evaluated to date by the DSMC, it is of interest that the mean SpO2 in the 2 Oximeter arms is 90% and 92%, with

medians of 92% and 94%, all of which are below that reported by Hagadorn et al (median=95). The 2 other relevant trials, STOP-ROP and BOOST, both enrolled infants at about 32 weeks PCA, and maintained 2 levels of SpO2, 89% to 94% and 91-94% versus 95% to 98% and 96% to 99%, by administration of oxygen. These studies achieved reasonable separation, but did demonstrate substantial overlap of the intended ranges. It is important to note that these studies were testing two ranges both of which were higher than the lower range of the SUPPORT trial (85% to 89%) and were treating infants who, for the most part, had recovered from their acute disease. In the BOOST trial 70% of the enrolled infants were < 28 weeks of age at birth (all of SUPPORT is < 28 weeks), 32 weeks postmenstrual age (PMA), and required oxygen at enrollment (Askie et al, New England Journal of Medicine. 2003; 349(10):959-967). The STOP-ROP trial enrolled infants with pre-threshold ROP at a PMA of 35.4 + 2.5 weeks of age (Phelps et al, Pediatrics. 2000; 105(2):295-310). These trials then gave the higher SpO2 range infants additional oxygen to increase their SpO2 to the desired range. STOP-ROP reported that the infants in the high range had an SpO2 > 95% for > 97% of the monitored time. These studies found an overall increase in pulmonary morbidity in the higher SpO2 range infants.

Examination of oximeter data from one if the NRN sites (Case Western, Walsh et al) obtained for an ongoing study evaluating infants similar to those enrolled in SUPPORT, and managed with conventional oximeters revealed that for the 9 infants for whom results were available that the percentage of time with and SpO2 > 95% was > 50%.

The oximetry algorithm that was designed for the SUPPORT trial is such that re-conversion of the altered oximeter values does not result in a discrete SpO2 number for every displayed value. SpO2 values, of 93%, 94% 95% and 96% will all be reconverted to a single value in one arm, while 84%, 85%, 86% and 87% will be reconverted to a single value in the other arm. This is a result of having the displayed values return to non-skewed SpO2 values at < 84% and > 96%, a safety design felt to be important by all involved in this trial (See Attached file USCD1). Thus the percentages reported to the DSMC for some of the ranges that include these values were not an accurate representation of the true values. However all values > 96% and < 84% are actual and do not require any conversion.

Percent of time of spent at SpO2 < 84% and > 96%
(RTI, Nov 29, 2005, 14:00 Hrs)

Range	High target (91-95)	Low target (85-89)
< 84%	8.51	16.62
> 96%	22.69	13.60

In the current SUPPORT study, an initial analyses utilizing only unaltered SpO2 values as shown above , ie those below 84% and above 96% have shown that one arm had an SpO2 > 96% for 13.6% versus 22.69% of the time for the comparison arm, and the durations of an SpO2 < 84% was also different at

16.62% versus 8.51%. The previously reported value of 36% duration of an SpO2 > 95% for one group represented an artifact of the conversion algorithm as described above. The values for SpO2s > 96% using unaltered data suggests that the SUPPORT trial to date has, if anything, reduced the duration of hyperoxia.

In addition, using these values which represent actual SpO2 values, we can state that the infants in this trial are spending approximately 70% of the time with a true SpO2 value between 84% and 96%. We believe that this is information is very encouraging, and suggests that if we are able to further improve adherence to the target ranges that we will achieve an adequate separation between the groups.

As part of the SUPPORT trial, we collect information about inhaled oxygen concentration 3 times a day for the first 14 days and daily thereafter. We believe that a more frequent documentation of inhaled oxygen will allow us to determine the actual duration of oxygen exposure. At the present an infant is considered to be receiving supplemental oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized as receiving supplemental oxygen for significant periods when they are actually in room air. This would result in durations of SpO2 greater than 95% that were felt to be modifiable and reported as such when in fact there is no effective treatment for such elevated SpO2s. In addition, we do not know if such SpO2s on room air are associated with any morbidity. From the SUPPORT study data analyses to date we know that infants in room air have SpO2s > 95% for 46% to 69% of the time.

In view of this design, we would suggest that all future analyses evaluate the ranges of <84% and >96% as those ranges that are considered to be low and high.

We believe that the SUPPORT trial will actually define the periods of time that ELBW infants spend with different ranges of SpO2, and that it is essential to collect this information. In addition, as our findings indicate a lower true percent of the time at SpO2 values >95%, and lower median SpO2 values than has previously been reported, we are in fact, reducing the time with high SpO2 values compared to usual care. The SUPPORT trial carefully evaluates risks, and we will be evaluating group differences for all important short and long term outcomes.

The SUPPORT trial methodology actively encourages all caretakers to keep SpO2 < 96% by having alarm limits set at 85% to 95%. These limits were utilized because it was felt that these represented current practice. The oximetry algorithms were designed to keep infants in the narrower target range of 88% to 92% with the realization that setting alarm limits at these values would severely increase the frequency of the alarms sounding. Nevertheless, our results to date suggest that we have decreased the expected percent of time > 95%, and in one group the value of 14% may be as low as is achievable in an actual clinical environment.

We believe that the SUPPORT study will define the durations of high and low SpO2 and will be able to determine if there is a threshold duration of either value that is associated with altered outcomes, and for this reason alone, the

SUPPORT trial will be very valuable. All of the procedures outlined below in response to your second concern will also allow us to further increase the percentage of time that the infants are in the maximally altered SpO2 ranges which we believe will further increase separation of these groups.

Response to Issue Number 2

There is concern that we have not achieved adequate separation by the current oximeters and study personnel. Reviewing the newest analyses available as described above, there are differences in the durations of low and high SpO2s between the 2 oximeter groups. In addition, a careful analysis of the most recent converted values demonstrates that the cumulative time spent with an SpO2 of 90% or less is 24.3% versus 43%, for the 2 oximeter groups, supporting the ability of the altered oximeters to produce differential SpO2 exposures. We do acknowledge that it would desirable to increase the percentage of time in the narrower target range and towards this end would propose the following changes to SUPPORT:

1. We will require documentation that the alarm limits are set and functional as per protocol every 4-6 hours. We have found that in some units the high alarms are being defeated, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned to the respiratory therapists, and this procedure is already being done in many NRN units.

2. We will immediately initiate a change in our data collection for FiO2. We will change the data form to indicate that the infant was either in oxygen for the entire 24 hours, and if not, will check off the actual hours of oxygen exposure, and we will continue with this from of data collection for the entire time that the infant is receiving oxygen. In the current protocol we collect such information 3 times a day for the first 14 days only and then daily thereafter. We believe that more frequent documentation will allow us to determine the actual time that an infant is in room air. At the present the infant is considered in oxygen if he/she requires oxygen for greater than intermittent use. This results in infants being categorized in oxygen for significant periods when they are in room air. While in room air, we cannot manipulate the SpO2, and thus knowledge of the true time in oxygen will produce a more accurate representation of oximetry results that are subject to care interventions.

3. We will initiate further training and in-service at all the sites to stress the importance of keeping the SpO2 alarm functional and at the limits of 85% and 95%. In the past these were guidelines, and we will now change the study manual and protocol to indicate these limits are now set by protocol and that violations will be documented. We will encourage all caretakers to aim for an SpO2 value of 90% and make every effort to educate caretakers to make smaller

adjustments in FiO2 and ensure that the infant is maintained between the 87% to 93%, the range with the maximal separation of the study oximeters. We will further facilitate the use of the 2 hour and 12 hour histograms showing the infants' actual ranges to provide feedback to the caretakers regarding the percentage of time in the target ranges.

4. We will develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation. We would hope that such changes – ie increasing the FiO2 in steps of 5% as opposed to much larger increases will decrease the resultant overshoots creating the high SpO2 values. This will be included in the revised manual of operations.

5. We will place bedside cards to indicate the target range.

6. We will initiate compliance monitoring visits coordinated by RTI to visit random sites. These visits had been planned, but had not yet been initiated. The teams will consist of a member of RTI and a study coordinator, and they will review the adherence to the protocol and any other relevant issues.

We thank the DSMC for their thoughtful concerns. We trust that our plans to move forward with the SUPPORT trial are acceptable to the DSMC. We are anxious to initiate the above changes, seek IRB approvals and re-activate this trial.

LATE BREAKER ABSTRACT SUBMISSION FORM

Abstracts and Payment must be RECEIVED by March 1, 2004

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Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation

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Background: Detailed data are not available regarding the actual versus intended SpO2 in infants born <28 weeks gestation (extremely premature newborns, EPNs) in the neonatal period during routine care. **Objective:** To document actual SpO2 in EPNs in the first 4 weeks of life during routine care and compare to the level recommended by local policy/guideline. **Design/Methods:** EPNs <96 hours old were enrolled in a prospective multicenter cohort study. Oximetry data were collected every 2 seconds with masked signal-extraction oximeters for 72 hours in each of the first four weeks of life. Data were compared to SpO2 range prescribed by local institutional policy. **Results:** 14 centers from 3 countries enrolled 78 infants with mean birth weight 863 g (SD 208 g) and mean gestational age 26 wk (SD 1.4 wk). Lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for median of 70 hours (25^{th}-75^{th} percentiles 67-71 hr) in each week. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25^{th}-75^{th} percentiles 91-97; range of study center medians 91-96). Centers ranged between 16-71% compliance with intended SpO2 range. Most noncompliance was above intended range. **Conclusions:** Compliance with intended SpO2 range during routine care varied substantially among participating centers, and was generally poor regardless of intended level. These data will assist quality improvement and education efforts, and will aid planning of prospective randomized trials examining level of oxygenation. **Disclosure:** Funded by the SPR Student Research Program; Fight for Sight/Prevent Blindness America; The Tufts-NEMC Research Fund; GCRC/Natl Center for Research Resources MO1-RR00054, and NEI K23 EY/HD00420. Oximeters provided by Masimo Corp.

Briefly describe the reason why the December deadline could not be met:
Study still in progress at December deadline, with only about 60% of enrollment achieved.

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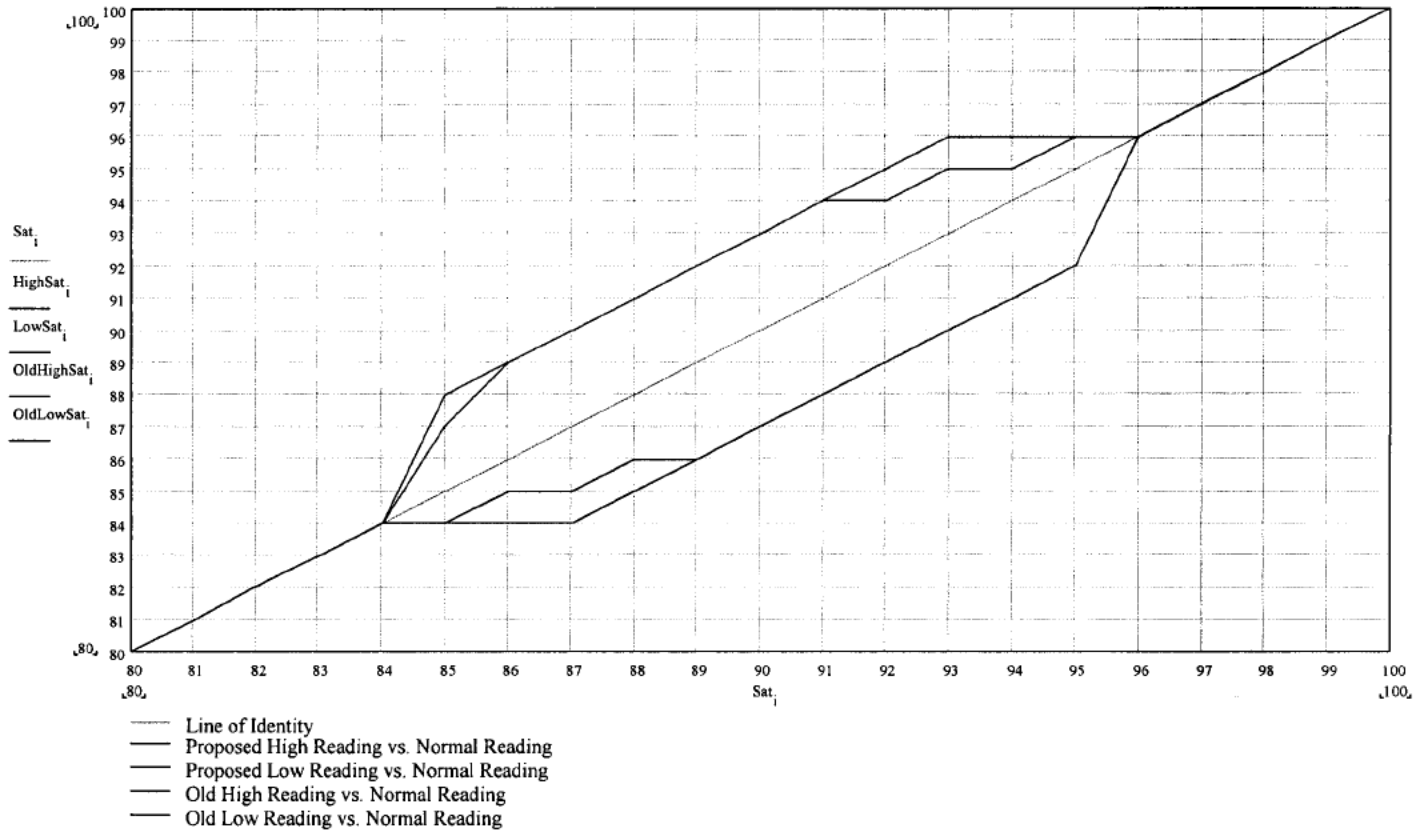
Converting Actual Readings to Low and High Readings

Actual Reading	To Low Reading	To High Reading
	85% -89%	91%-95%
100	100	100
99	99	99
98	98	98
97	97	97
96	96	96
95	92	96
94	91	96
93	90	96
92	89	95
91	88	94
90	87	93
89	86	92
88	85	91
87	84	90
86	84	89
85	84	88
84	84	84
83	83	83
82	82	82
81	81	81
80	80	80
etc	etc	etc



The Low, Actual & High Reading oximeters synchronize for values greater than or equal to 96 % and less than or equal to 84 %.

In the Actual range of 87 % to 95 %, the Low Reading Oximeter displays a value 3 points below actual.

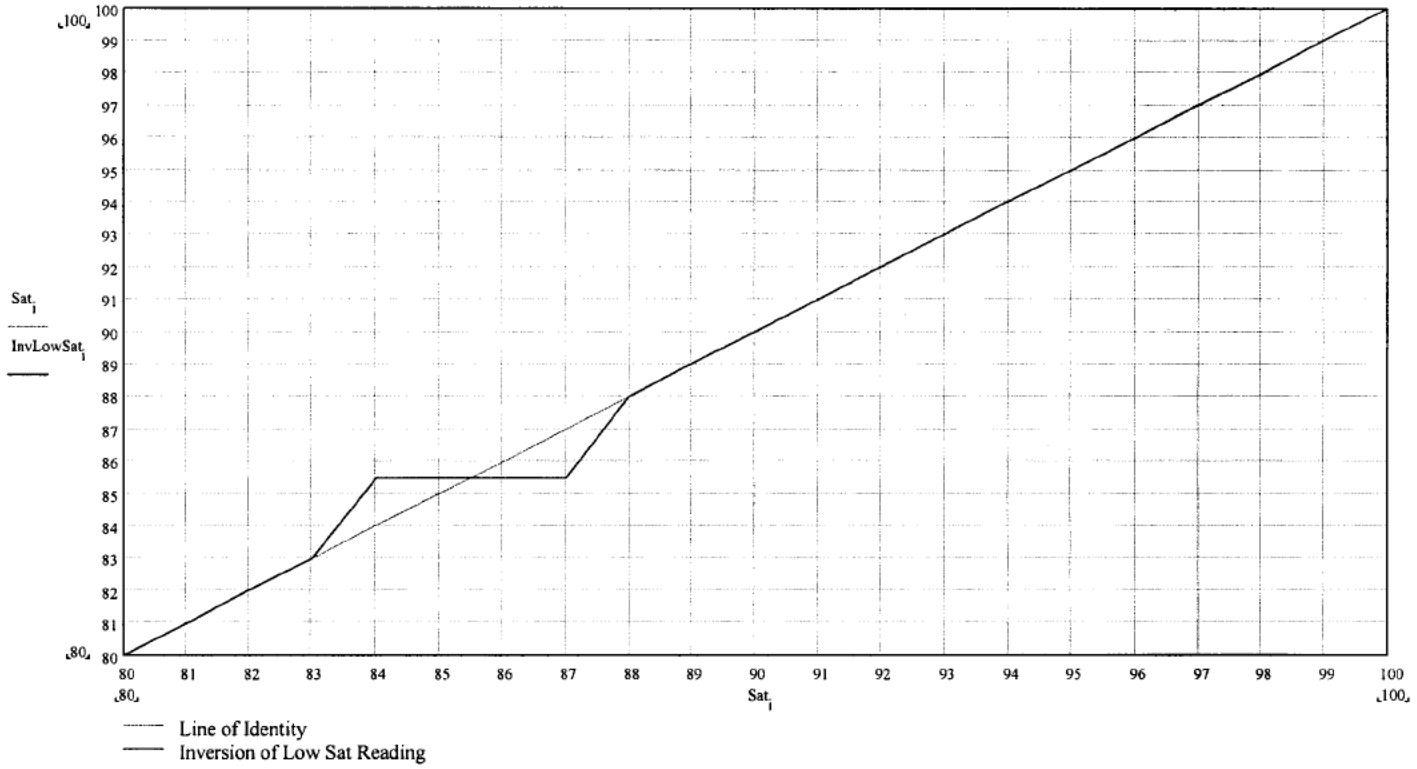
In the Actual range of 85 % to 93 %, the High Reading Oximeter displays a value 3 points above actual.

Converting Low Readings to Normal Readings

91% - 95%

Low Reading	To Normal Reading
100	100
99	99
98	98
97	97
96	96
95	95.75
94	95.50
93	95.25
92	95
91	94
90	93
89	92
88	91
87	90
86	89
85	88
84	85.5
83	83
82	82
81	81
80	80
etc	etc

There is no normal for values of 87%, 86%, 85%
All displayed values > 92% are equated with 96%
Thus 96% is overrepresented
96% can represent any displayed value of 93-96%, there will be actual values of 96%, these can be distinquished by the decimal point values
Applying the above inversion yields the following performance:



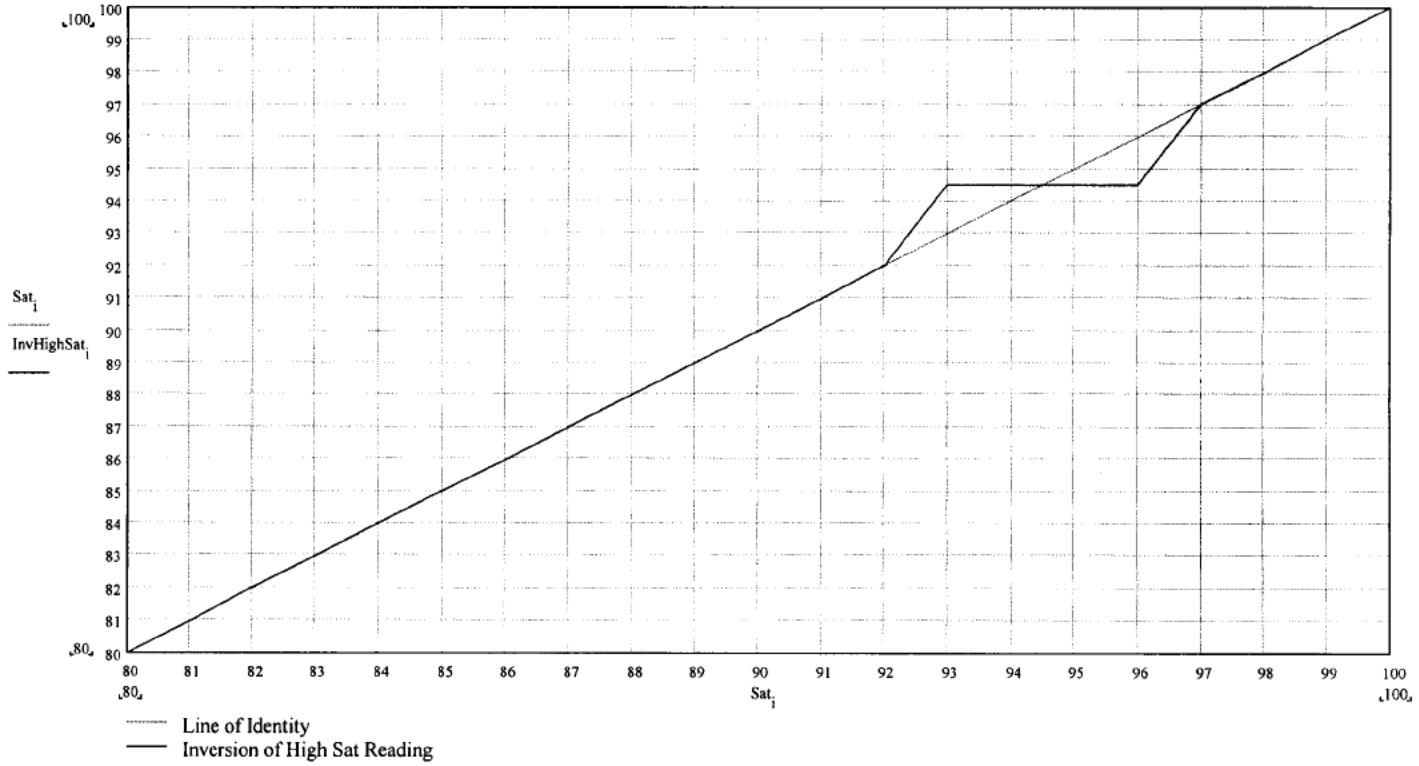
The inversion has no error above and below an actual reading of 88 % and 83 %, respectively. In between these limits, the inversion error does not exceed 1.5 %. Subjects are typically kept in the region of 91 % (88 % + 3 %) to 95 % (92 % + 3 %).

Converting High Readings to Actual Readings

85% - 89%

High Reading	To Actual Reading
100	100
99	99
98	98
97	97
96	94.5
95	92
94	91
93	90
92	89
91	88
90	87
89	86
88	85
87	84.75
86	84.50
85	84.25
84	84
83	83
82	82
81	81
80	80
etc	etc

No actual values of 93%, 94% 95% or 96%. These are all represented by 94.5%
All displayed values of 87%, 86% 85% 84% are converted to 84%
Thus 84% is overrepresented as 94.5%
Applying the above inversion yields the following performance:



The inversion has no error above and below an actual reading of 97 % and 92 %, respectively. In between these limits, the inversion error does not exceed 1.5 %. Subjects are typically kept in the region of 85 % (88 % - 3 %) to 89 % (92 % - 3 %).

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Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), A Randomized, Controlled Trial. I: Primary Outcomes

The STOP-ROP Multicenter Study Group

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Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), A Randomized, Controlled Trial. I: Primary Outcomes

The STOP-ROP Multicenter Study Group*

ABSTRACT. *Objective.* To determine the efficacy and safety of supplemental therapeutic oxygen for infants with prethreshold retinopathy of prematurity (ROP) to reduce the probability of progression to threshold ROP and the need for peripheral retinal ablation.

Methods. Premature infants with confirmed prethreshold ROP in at least 1 eye and median pulse oximetry <94% saturation were randomized to a conventional oxygen arm with pulse oximetry targeted at 89% to 94% saturation or a supplemental arm with pulse oximetry targeted at 96% to 99% saturation, for at least 2 weeks, and until both eyes were at study endpoints. Certified examiners masked to treatment assignment conducted weekly eye examinations until each study eye reached ophthalmic endpoint. An adverse ophthalmic endpoint for an infant was defined as reaching threshold criteria for laser or cryotherapy in at least 1 study eye. A favorable ophthalmic endpoint was regression of the ROP into zone III for at least 2 consecutive weekly examinations or full retinal vascularization. At 3 months after the due date of the infant, ophthalmic findings, pulmonary status, growth, and interim illnesses were again recorded.

Results. Six hundred forty-nine infants (325 conventional and 324 supplemental) were enrolled from 30 centers over 5 years. Five hundred ninety-seven (92.0%) infants attained known ophthalmic endpoints, and 600 (92%) completed the ophthalmic 3-month assessment. The rate of progression to threshold in at least 1 eye was 48% in the conventional arm and 41% in the supplemental arm. After adjustment for baseline ROP severity stratum, plus disease, race, and gestational age, the odds ratio (supplemental vs conventional) for progression was .72 (95% confidence interval: .52, 1.01). Final structural status of all study eyes at 3 months of corrected age showed similar rates of severe sequelae in both treatment arms: retinal detachments or folds (4.4% conventional vs 4.1% supplemental), and macular ectopia (3.9% conventional vs 3.9% supplemental). Within the prespecified ROP severity strata, ROP progression rates were lower with supplemental oxygen than with conventional oxygen, but the differences were not statistically significant. A post hoc subgroup analysis of plus disease (dilated and tortuous vessels in at least 2 quadrants of the posterior pole) suggested that infants without plus disease may be more responsive to supplemental therapy (46% progression in the conventional arm vs 32% in the supplemental arm) than infants with plus disease (52% progression in conventional vs 57% in supplemental).

Pneumonia and/or exacerbations of chronic lung disease occurred in more infants in the supplemental arm (8.5% conventional vs 13.2% supplemental). Also, at 50 weeks of postmenstrual age, fewer conventional than supplemental infants remained hospitalized (6.8% vs 12.7%), on oxygen (37.0% vs 46.8%), and on diuretics (24.4% vs 35.8%). Growth and developmental milestones did not differ between the 2 arms.

Conclusions. Use of supplemental oxygen at pulse oximetry saturations of 96% to 99% did not cause additional progression of prethreshold ROP but also did not significantly reduce the number of infants requiring peripheral ablative surgery. A subgroup analysis suggested a benefit of supplemental oxygen among infants who have prethreshold ROP without plus disease, but this finding requires additional study. Supplemental oxygen increased the risk of adverse pulmonary events including pneumonia and/or exacerbations of chronic lung disease and the need for oxygen, diuretics, and hospitalization at 3 months of corrected age. Although the relative risk/benefit of supplemental oxygen for each infant must be individually considered, clinicians need no longer be concerned that supplemental oxygen, as used in this study, will exacerbate active prethreshold ROP. *Pediatrics* 2000;105:295–310; *retinopathy of prematurity, oxygen therapy, visual loss, oxygen toxicity, prematurity, neonatal outcomes, bronchopulmonary dysplasia.*

From the STOP-ROP Multicenter Study Group.
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ABBREVIATIONS. ROP, retinopathy of prematurity; CRYO-ROP,

cryotherapy for ROP; STOP-ROP, Supplemental Therapeutic Oxygen for Prethreshold ROP; PMA, postmenstrual age; SES, socioeconomic status; CLD, chronic lung disease; CPAP, continuous positive airway pressure; OR, odds ratio; CI, confidence interval.

Retinopathy of prematurity (ROP) is a neovascular retinal disorder that develops in 84% of premature survivors born at <28 weeks' gestation. Fortunately, ROP resolves in most cases (80%) without visual loss from retinal detachments or scars.[1,2] The multicenter study of cryotherapy for ROP (CRYO-ROP) study showed that, when the disorder progresses, ablation of the avascular peripheral retina with cryotherapy reduced the incidence of retinal detachment from 51% to 31%.[3] Peripheral retinal ablation, now usually by laser therapy, has become standard treatment for advanced ROP.[4–7] However, this therapy is not always successful in halting the progression of ROP, and the long-term complications of extensive ablation of the developing peripheral retina beyond 5 years of age[7] are as yet unknown.

In 1948, Michaelson[8] proposed that a gradually increasing oxygen deficit of the oxygen-consuming retina during normal differentiation causes release of an angiogenic growth factor. Based on this supposition, therapeutic administration of supplemental oxygen to relieve the putative hypoxic stimulus for retinal neovascularization has been considered. In the 1950s, Szewczyk[9] and Bedrossian et al[10,11] first reported the use of supplemental oxygen to treat the neovascularization in ROP. This approach was abandoned after the 1956 Cooperative Study of Retrolental Fibroplasia demonstrated that prolonged (4 weeks) administration of 50% oxygen caused increased rates of ROP and vision loss.[12] But the concept of an hypoxic stimulus for retinal neovascularization remained biologically plausible and eventually regained scientific interest and attention.

Case–control studies revealed that infants who develop severe ROP, compared with infants of similar gestation and birth weight who do not have ROP, have hospital courses characterized by more complex medical problems, prolonged oxygen requirements, lower overall arterial oxygenation levels, and more episodes of fluctuating blood oxygen levels.[13–15] In contrast to healthy neonates breathing room air, whose arterial oxygen levels are similar to those of adults (95–100 mm Hg [13 pKa]), the recommended arterial concentrations for premature infants receiving oxygen are 50 to 80 mm Hg (6.6–10.6 kPa).[16] This relative hypoxia in premature infants raised the possibility that supplemental oxygen might be used to improve retinal oxygenation and down-regulate retinal neovascularization. Tests of the effects of such oxygen supplementation in animal models of ROP supported this hypothesis,[17,18] and a reported benefit of supplemental oxygen in a clinical case series[19] provided additional support for systematically testing the hypothesis in premature infants with ROP. We report the primary results from the Supplemental Therapeutic Oxygen for Prethreshold ROP (STOP-ROP) study, which was designed to test the hypothesis that supplemental oxygen, given to attain a pulse oximetry range of 96% to 99% saturation, would reduce by one third the proportion of infants with at least 1 eye progressing from moderate ROP (prethreshold) to threshold ROP requiring peripheral ablative surgery, without unacceptable side effects.[20]

METHODS

Study Design

The study design was a randomized trial comparing the effects of 2 oxygenation strategies on the progression of ROP: conventional oxygenation at a pulse oximetry target of 89% to 94% versus supplemental oxygen to achieve a pulse oximetry target range of 96% to 99%.[21] From February 1994 to March 1999, eligible patients from 30 centers were typically enrolled by telephone call to the central coordinating center (64%) after confirmation of eligibility and signed informed consent by parents or legal guardians. Random assignments were generated by the coordinating center using the Wei-Lachin Urn Scheme[22] and were stratified by center and by 2 levels of baseline ROP severity. When the coordinating center was not available, study centers used sequentially numbered, sealed envelopes provided in advance by the coordinating center to obtain treatment assignments, and submitted appropriate documentation to the coordinating center. An infant was assigned to the severe ROP stratum A whenever either study eye had 1 or more clock hours of any stage ROP in zone I, or when the fellow eye was already at threshold or worse ROP (see Table 1), thereby eliminating that eye as a study eye. The remaining infants fell in the less severe ROP stratum B with zone II prethreshold ROP in both eyes or in the second eye at less than prethreshold ROP. Family, bedside nurses, and attending neonatologists knew the treatment assignment, but the study-certified ophthalmologists who assessed eligibility, progression of the ROP, and study end-

TABLE 1. Definitions of ROP Severity Categories for STOP-ROP

Threshold ROP*	
Zone II	Presence of posterior pole dilation/tortuosity in at least 2 posterior pole quadrants (plus disease), and stage 3 ROP for at least 5 contiguous clock h or 8 composite clock h
Zone I	ROP (any stage) with posterior pole dilation/tortuosity in at least 2 posterior pole quadrants (plus disease), or stage 3 ROP, with or without plus disease
Beyond threshold	Stage 4 ROP, stage 5 ROP, or massive vitreal hemorrhage obscuring the view of the fundus
Prethreshold ROP	
Zone II	Any number of clock hours of stage 3 ROP, less than threshold severity, or any stage 2 ROP with at least 2 quadrants of posterior pole dilation/tortuosity disease (plus disease)
Zone I	Any ROP less than threshold severity

Stages and zones based on the international classification of ROP.[24]

* The definition of threshold ROP differs somewhat from that used in the CRYO-ROP study[4] in 2 ways: 1) In the CRYO-ROP study, "plus disease" was a global assessment of the posterior pole and was not determined according to number of quadrants involved, and 2) in the CRYO-ROP study, the definition of threshold was the same for both zone I and zone II and is the same as stated for zone II above (except for the number of quadrants of posterior pole dilation/tortuosity, as described in note 1). In STOP-ROP, a less stringent definition of threshold in zone I was used to accommodate the clinical judgment of a majority of the participating ophthalmologists that earlier treatment was needed to improve the poor outcomes of zone I threshold ROP.

points remained masked to treatment assignment throughout the study.

The primary endpoint of this study of systemic oxygen therapy was based on the infant, ie, progression of at least 1 study eye of an infant to threshold ROP (Table 1). Infants had only 1 study eye if the fellow eye was already at threshold or worse than threshold ROP at enrollment. Otherwise, they had 2 study eyes; even a fellow eye at less than prethreshold severity was considered a study eye, because it was going to be exposed to the assigned treatment and could progress to threshold ROP. Secondary endpoints included ophthalmic status at 3 months after due date, infant growth rates, developmental screening, and adverse medical events. The protocol was reviewed and approved by the institutional review board at each participating site before initiation of recruitment at that site.

Eligibility Criteria

Premature infants were screened for ROP, according to local guidelines consistent with the 1992 recommendations of the American Academy of Pediatrics,[16] at 71 hospitals affiliated with 30 certified participating centers throughout the United States. Infants with prethreshold ROP in at least 1 eye (Table 1) were registered as potentially eligible for the study and monitored for a minimum of 4 hours with continuous pulse oximetry. Registered candidates were excluded as ineligible whenever their median pulse oximetry was greater than 94% saturation while breathing room air or they had lethal anomalies or congenital anomalies of the eye. The family or guardian of eligible infants was approached for consent if the attending neonatologist agreed that randomization to either oxygen saturation target range could be achieved and would be medically safe, and that the infant's caretaker would be able to comply with the follow-up appointments. The diagnosis of prethreshold ROP in at least 1 eye then had to be confirmed independently by a second examiner to qualify for randomization. At least 1 of the 2 examiners had to be certified by the STOP-ROP study; usually both were.

Intervention

Although randomization and initiation of treatment within 24 hours of the diagnosis of prethreshold ROP was the goal, later enrollment was permitted as long as at least 1 eye was verified as remaining at prethreshold within the preceding 48 hours. The treatment assignment was for the infant to be placed on continuous pulse oximetry monitoring and to maintain oxygen saturation, as much as possible, in the target range of either 89% to 94% (conventional) or 96% to 99% (supplemental). Ohmeda 3740 pulse oximeters and laptop computers with software to monitor, record, and report trends in oxygen saturation were provided by the study for each infant. The Ohmeda 3740 pulse oximeter is calibrated at the factory to display a saturation lower by 1.6 saturation points, compared with other commercial oximeters, to correct for assumed carboxyhemaglobin and methemaglobin levels. Oximeters provided continuous data to a laptop computer that displayed real-time oxygen saturation summary graphs and tables updated every 20 seconds. The percent time in the assigned target range over varying time periods was displayed (Fig 1). Whenever the oxygen saturation was out of the target range for >10 of the previous 20 minutes and the saturation was currently out of range, the computer produced a unique alarm. The alarm limits on the oximeter itself were set according to the each hospital's usual policy. Using this continuous feedback, the bedside nurse or family could readily make necessary adjustments to the oxygen environment to maximize the time spent in the assigned target range. Pulse oximetry values were recorded to a computer disk every 40 seconds during the weeks the infant was on study equipment.

Study saturation targets continued for a minimum of 2 weeks, even if ophthalmic endpoints were reached in both eyes sooner. After those 2 weeks, treatment assignment and equipment were stopped after both eyes reached ophthalmic endpoints. Brief periods off equipment were allowed for procedures or baths. Occasionally an infant was ready for discharge home before reaching study endpoint in both eyes. The parents or guardians were then trained to use the study oximeter and computer to permit the assigned treatment to be continued, recorded, and completed at home.

Outcome Variables

Study-certified ophthalmologists and study center coordinators examined enrolled infants weekly until both eyes reached oph-

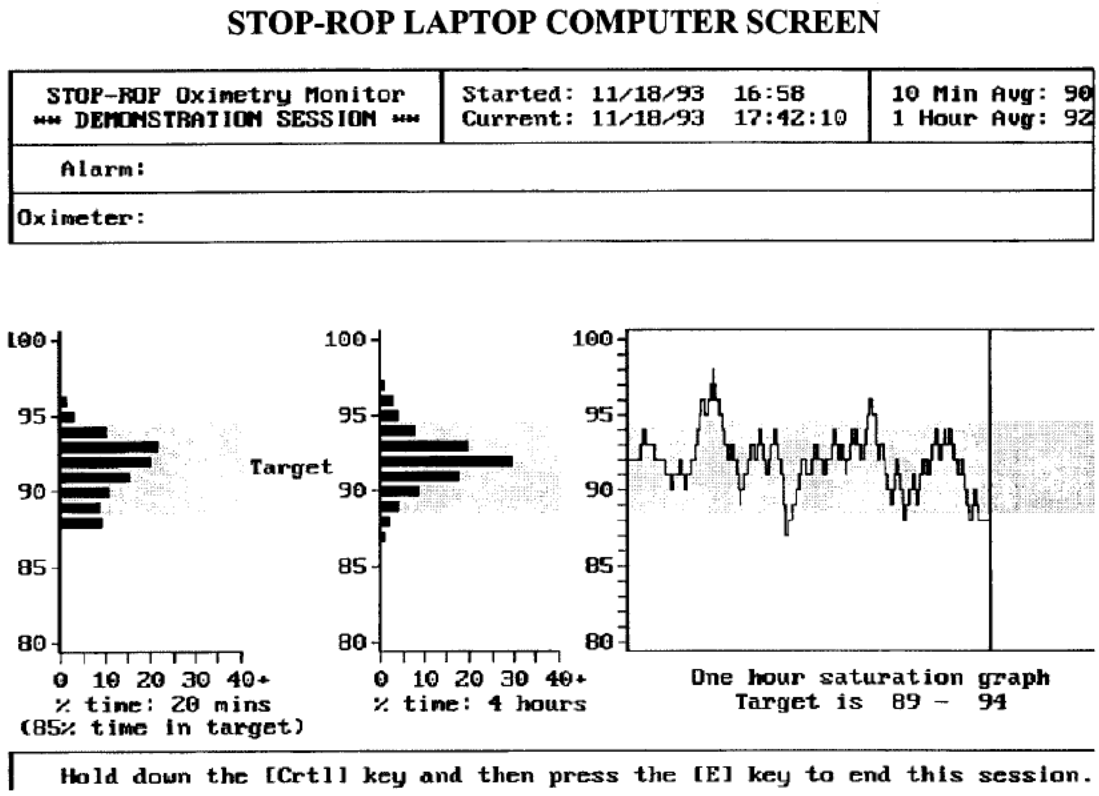

Fig 1. Computer screen format. Frequency distributions and oximetry strip chart information provided continuously at the bedside for nursing management of the pulse oximetry study targets. In this sample, the infant is assigned to the conventional arm (89%–94% saturation), the area highlighted in gray.

thalmic endpoints and again at 3 months' corrected age (that is, 3 months past the term due date of 40 weeks' postmenstrual age [PMA]). The computers and oximeters were covered during examinations to maintain masking of the ophthalmologists. To standardize diagnoses, all ophthalmologists were certified in the completion of study data forms. If they had not been previously certified during the acute phase of the CRYO-ROP or Light Reduction-ROP studies,[23] their use of the international classification of ROP[24] was certified by study headquarters through a series of dual examinations of infants with ROP. Standard fundus photographs of degrees of severity of posterior pole dilation/tortuosity were provided to each center for use at the bedside to promote uniformity of the diagnosis (Fig 2). For the STOP-ROP study, plus disease was defined as "at least 2 quadrants of dilation and tortuosity of the posterior pole vessels." Study personnel completed annual recertification throughout the study.

An adverse ophthalmic endpoint was defined as progression to threshold ROP (or worse), diagnosed by 1 study-certified ophthalmologist and confirmed independently by a second study-certified ophthalmologist. Eyes confirmed to have reached threshold ROP were referred for possible cryotherapy or laser therapy. The definition of threshold ROP (Table 1) in zone II was the same as that used by the CRYO-ROP study; however, in zone I, the definition was modified to permit a diagnosis of threshold at slightly less severity of ROP than required by the CRYO-ROP study because zone I threshold ROP, as defined in CRYO-ROP, progressed to poor retinal outcomes in 78% of eyes even with cryotherapy.[3]

A favorable ophthalmic endpoint was defined as regressing ROP in zone III for at least 2 successive weekly examinations, or full retinal vascularization. Ophthalmic outcomes at 3 months' corrected age were classified as: 1) unfavorable when there were findings of total or partial retinal detachment or when the visual axis was otherwise obstructed, 2) indeterminate when there was macular ectopia, or 3) favorable when there were only minor peripheral findings, laser or cryotherapy scars, or active ROP in zone II or III. The uncommon finding of continued active ROP at 3 months' corrected age was followed whenever possible with a repeat examination at 6 months' corrected age, although this situation had not been anticipated when the STOP-ROP protocol was developed. Whenever missed examinations or death caused incomplete endpoint dating or diagnosis of an eye's endpoint, all available eye data were provided to an ophthalmic endpoints committee of 3 ophthalmologists masked to the treatment assignment. The committee reached consensus on the outcome of each eye according to the following categories: 1) almost certainly reached adverse ophthalmic endpoint, 2) may have reached adverse ophthalmic endpoint, 3) indeterminate, 4) may have reached favorable ophthalmic endpoint, or 5) almost certainly reached favorable ophthalmic endpoint. Only consensus votes of 1 or 5 were used in any subsequent secondary analyses, and the committee was unaware of this analysis decision when they met (votes 2, 3, or 4 were treated as unknown).

Pediatric data were recorded at the time of randomization, at weekly intervals throughout the intervention period, and again at 3 months' corrected age. These data included duration of oxygen use and hospitalization after randomization; weight, length, and head circumference; use of diuretics, methylxanthines, or steroids; a checklist of specified adverse events; and episodes of rehospitalization. The age for achieving full nipple feeds was determined as the first day of 3 consecutive days of taking all enteral feedings by mouth. The questions for the Hollingshead classification of socioeconomic status (SES) were asked at discharge.[25] Adverse events, rehospitalizations, and deaths before 3 months' corrected age were reported as they occurred. The Revised Parental Denver Questionnaire was administered at 3 months' corrected age.[26]

All deaths and rehospitalizations were reviewed by 3 neonatologists masked to treatment assignment to determine whether pulmonary disease was the primary cause of death or rehospital-

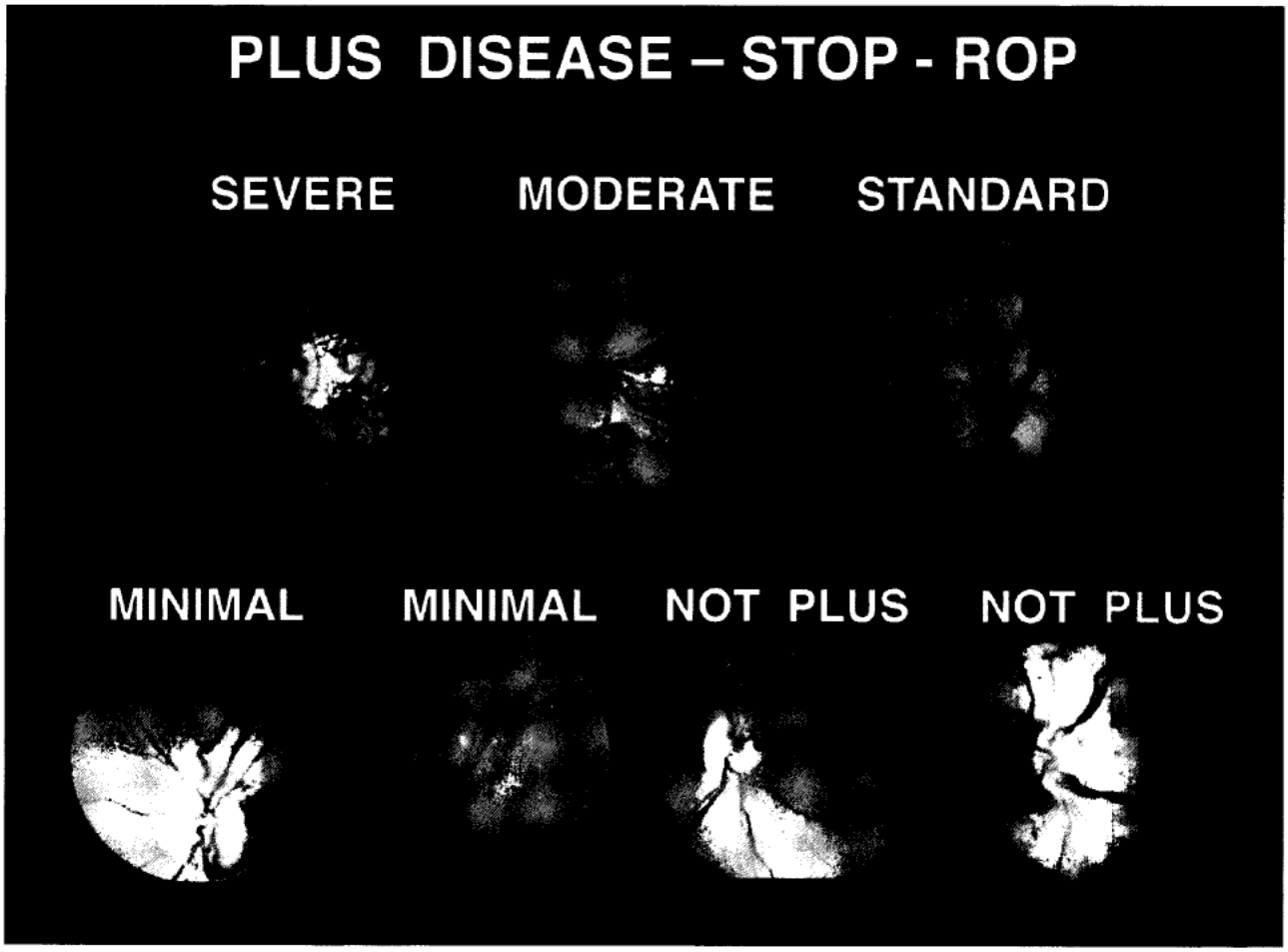

Fig 2. Standard photographs for the STOP-ROP study: fundus photographs of the posterior pole (visible with a direct ophthalmoscope), showing examples of mild to moderate posterior pole dilation/tortuosity and samples of retinas without this finding.

ization. Pneumonia/chronic lung disease (CLD) events were defined as probable or definite pneumonia, an acute exacerbation of CLD, or some combination of these 2 such that the study neonatologist could not distinguish between them.

Pulmonary Score

A composite pulmonary score was developed to describe the pulmonary status of each infant at baseline. The pulmonary score was calculated as:

$$\text{Pulmonary score} = (F_{IO_2})\,(\text{support}) + (\text{medications})$$

where F_{IO_2} is expressed as a fraction (room air = .21); support = 2.5 if on ventilator, 1.5 if on nasal or endotracheal continuous positive airway pressure (CPAP), and 1.0 if on nasal cannula, hood oxygen or off oxygen; and medications = .05 each for methylxanthines or intermittent diuretics, .10 for daily diuretics, .10 for inhaled steroids, and .20 for systemic steroids for CLD. Therefore, the pulmonary score could have a range of values between .21 (no pulmonary support, oxygen, or medications) and 2.85 (assuming that an infant would not be on both inhaled and systemic steroids). The baseline pulmonary score correlated well with pulmonary rehospitalizations, pulmonary deaths, and markers of CLD severity, such as duration of oxygen therapy (data not shown).

Sample Size and Data Monitoring

The progression rate to threshold was monitored by the Data and Safety Monitoring Committee at annual meetings. An early stopping guideline was constructed for ophthalmic benefit at an overall α-value of .025, and a stopping guideline for ophthalmic harm at an overall α-value of .10, allowing for repeated interim analyses[27] using the software of Reboussin (Madison, WI, University of Wisconsin, Department of Statistics). A sample size of 880 infants (to achieve 816 cases with final outcome data) was calculated as necessary to provide 90% power with an overall type I error rate of .025 to detect a one third reduction in progression to threshold disease or a 10% absolute reduction based on a predicted rate of progression of 30% in the conventional arm.[1] Adverse events were reviewed biweekly, and deaths were reviewed immediately by a neonatologist on the Data and Safety Monitoring Committee. All adverse events were reviewed at each meeting of the full Committee.

In 1997, the Data and Safety Monitoring Committee, after the enrollment of 449 children over 3.3 years, expressed concern about the ability of the study group to enroll the target number of 880 infants within 5 years, given consistent enrollment rates averaging 11.2 infants per month. Furthermore, new reports of nonrandomized case series in human infants suggesting a strong beneficial effect of supplemental oxygen,[28,29] as well as publication of additional animal model data,[30–35] supported the hypothesis of the STOP-ROP study, which might adversely affect enrollment. Calculations at that time showed that an enrollment of 633 infants completing the study would provide 83% power to detect a fall in the progression rate from 30% to 20%. The Committee members, who were not masked to study ophthalmic outcomes (although masked to treatment assignment) at the time of the review, recommended that recruitment continue through March 1999 with a revised enrollment goal of at least 633 infants. The final number of 649 enrollees, with ophthalmic endpoints available for 597, resulted in a power of ~80% against the designed alternative.

Statistical Analyses

Primary analyses were performed on all enrollees according to the assigned treatment arm (intention-to-treat) using the group-sequential method of Kim and DeMets.[27] Secondary categorical characteristics of the patients in the 2 arms were compared by χ^2 test, and group differences of continuous factors were compared with Student's t test and Wilcoxon rank-sum test. Logistic regression was used for the adjustment of progression rates for covariates. All P values presented are 2-sided and are unadjusted for the 5 interim examinations of the data, ie, are nominal P values, unless otherwise specified. Analyses were conducted with SAS software (SAS Institute, Cary, NC).[36]

RESULTS

Patients

Comparability of Enrolled and Registry Infants

From February 9, 1994, through March 31, 1999, 1847 infants with prethreshold ROP in at least 1 eye were registered at the participating centers. Of these, 634 (34%) were ineligible because either their pulse oximetry was greater than 94% in room air, or they had fatal or congenital eye anomalies (Fig 3). Of 1213 clinically eligible infants, 649 (54%) were enrolled. Reasons for nonenrollment were refusals of the family/guardians or the neonatologist (368), nonconfirmed prethreshold ROP (41), enrollment in conflicting studies (9), judgment that the infant was too ill to attempt randomization to the supplemental arm (28), inability of the family to comply with follow-up visits (41), imminent transfer to another hospital (8), and others. Of the ineligible infants, 99% had pulse oximetry greater than 94% in room air. Nonenrolled infants, including both those ineligible and those eligible but not enrolled (1198), weighed more at birth than enrolled infants (787 ± 287 vs 726 ± 160 g; $P < .001$) and had a slightly higher gestation at birth (25.7 ± 1.8 vs 25.4 ± 1.5 weeks; $P < .01$).

Comparability of Treatment Arms

Of the enrolled infants, 325 were randomized to the conventional arm, 324 to the supplemental arm, and their study completion rates are shown in Fig 3. The primary ophthalmic endpoint was available for 597 (92%) and was not recorded for 52 infants because of death (2), parental withdrawals from the study treatment (18), treatment with cryotherapy/laser before reaching ophthalmic endpoints (5), and missed eye examinations (27). Ophthalmic evaluations at 3 months' corrected age were completed for 600 infants and were unavailable for 49 because of death (16), withdrawal (31), and loss to follow-up (2). (Three additional infants in the supplemental arm not shown in the figure returned for just the neonatal portion of the 3-month evaluation). Rates of noncompletion were similar for both treatment arms (Fig 3).

Baseline demographic and pediatric characteristics are shown in Table 2, and ophthalmic baseline characteristics in Table 3. Randomization resulted in similar groups. Enrollment and randomization occurred at a PMA (PMA = gestational age at birth plus chronological age) of 35.4 ± 2.5 weeks (range: 30–48 weeks). The baseline pulmonary severity score and the mode of oxygen support were similar between the 2 arms. Many infants were on diuretics (54%) and methylxanthines (70%), and 29% had received steroids for CLD in the week before enrollment.

The ophthalmic baseline characteristics shown in Table 3 were also similar between the conventional and supplemental arms. There were no significant differences between the treatment arms in the number of infants enrolled in each ROP severity stratum or substratum. For the more severe forms of ROP represented in stratum A, 4.3% of enrollees had 1 eye at or beyond threshold (therefore, only 1 study eye), and 23.4% had 1 or both eyes with at least 1 clock hour of ROP in zone I. In stratum B, infants with

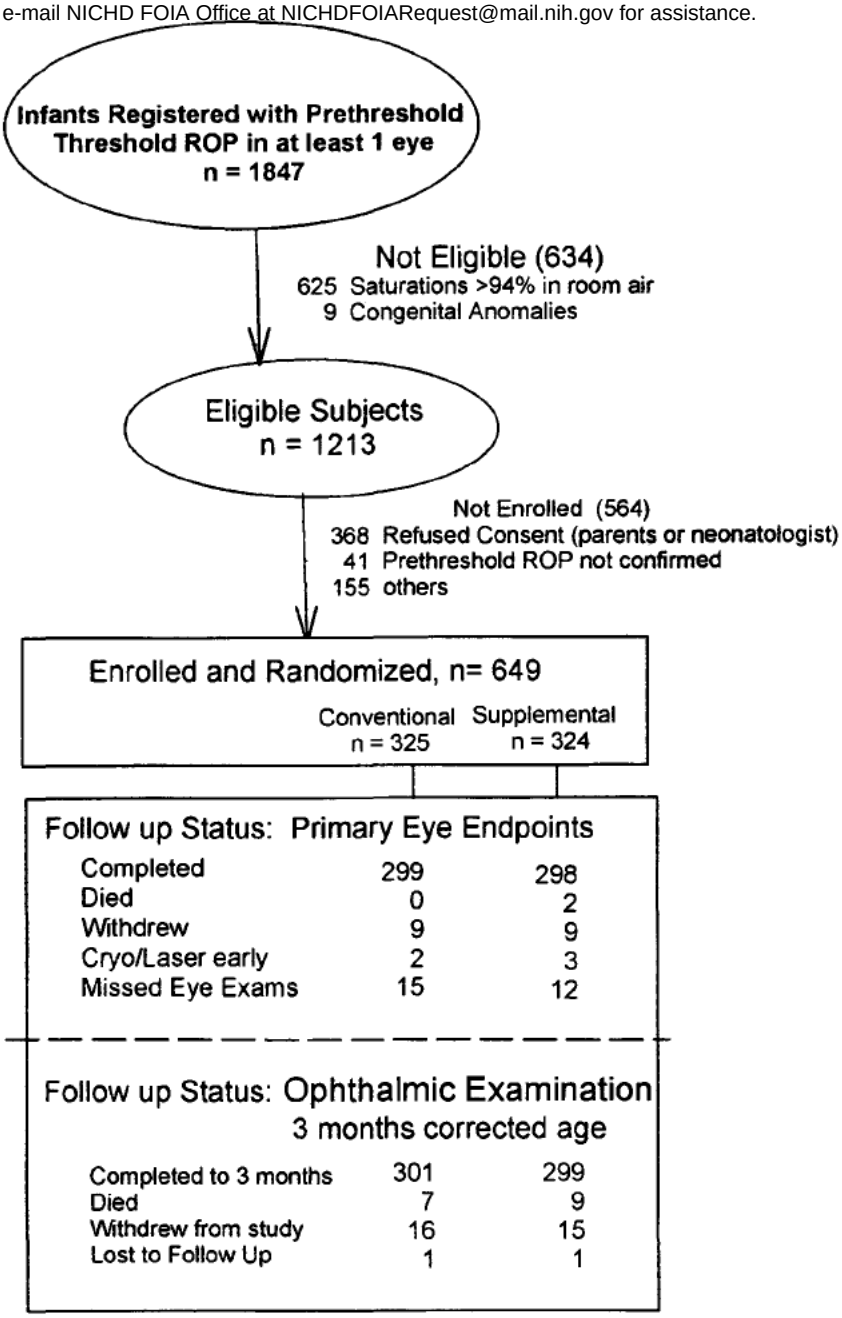

Fig 3. Patient enrollment flow diagram. There were several subjects without primary ophthalmic endpoints who nonetheless continued with follow-up examinations; therefore, there are more completed 3-month examinations than primary ophthalmic endpoints. Three additional supplemental infants completed the 3-month neonatal outcome examination, although they failed to complete the ophthalmic 3-month examination (not shown in figure).

zone II ROP in both eyes comprised 51% of all enrollees, and the remaining 21% entered the trial with the prethreshold eye's fellow eye at less than prethreshold ROP. There were no significant differences between the 2 arms in the number randomized within the first 24 hours after observing prethreshold ROP and in the numbers randomized after a longer period (Table 3). The elapsed time from the first diagnosis of prethreshold ROP to randomization was <24 hours in 33% of infants and >48 hours in 27% of infants.

Adherence to the Protocol

Oxygen requirements increased significantly for the infants randomized to the supplemental range. The average oxygen concentration increased from 36% ± 14% pretreatment to 46% ± 20%, 24 hours after randomization for those infants on a ventilator, CPAP, or hood oxygen; the average increase was 9.5% ± 16.5%. For infants on nasal cannula, the interactions between flow, infant size, and the oxygen concentration administered by cannula made estimation of the change in oxygen concentration more complex. Using the conversion formula of Benaron and Benitz,[37] average transformed oxygen concentration for infants on nasal cannula rose from 26% ± 6% before, to 31% ± 11% 24 hours after randomization to the supplemental arm; the average increase was 5% ± 9%. During the same 24-hour period, infants assigned to the conventional arm experienced a change from 36% ± 17% to 32% ± 15% in the infants on a ventilator, CPAP, or hood oxygen, and from 28% ± 10% to 26% ± 11% in the nasal cannula infants. (The 53 conventional and 25 supplemental

TABLE 2. Baseline Characteristics of Enrollees

	Number Enrolled		
	Conventional 325	Supplemental 324	Totals 649
Birth weight (g)*	721 ± 160	731 ± 161	726 ± 160
Gestational age (wk)*	25.4 ± 1.5	25.4 ± 1.5	25.4 ± 1.5
PMA (wk)*	35.3 ± 2.6	35.4 ± 2.5	35.4 ± 2.5
Weight at entry (g)*	1538 ± 445	1556 ± 442	1547 ± 443
Gender (% male)	53.9%	60.5%	57.2%
Race			
White	180 (55%)	179 (55%)	359 (55%)
Black	91 (28%)	101 (31%)	192 (30%)
Hispanic	31 (10%)	26 (8%)	57 (9%)
Others	23 (7%)	18 (6%)	41 (6%)
Pulmonary status			
Pulmonary score*	.53 ± .36	.56 ± .37	.55 ± .37
Ventilator	46 (14%)	57 (18%)	103 (16%)
CPAP or hood	57 (18%)	55 (17%)	112 (17%)
Nasal cannula	210 (64%)	203 (63%)	413 (64%)
No oxygen	12 (4%)	9 (3%)	21 (3%)
Medications			
Methylxanthines	68.6%	72.5%	70.1%
Diuretics	52.3%	57.1%	54.1%
CLD steroids†	28.1%	30.6%	29.3%
SES‡			
High (35–66)	27%	27%	27%
Intermediate (20–34)	30%	29%	29%
Low (0–19)	29%	26%	27%
Missing	14%	19%	16%

* Mean ± standard deviation.
† Steroids given systemically for CLD within the past week, not including inhaled steroids. Excludes 33 conventional and 40 supplemental infants from the early months of the study when data on the use of steroids were not being collected.
‡ SES by Hollingshead criteria,[25] as assessed at discharge.

TABLE 3. Baseline Ophthalmic Characteristics By Treatment Group

Characteristic	Conventional		Supplemental		Total	
	n	%	*n*	%	*n*	%
	325	100%	324	100%	649	100%
Stratum A—at least 1 eye PT ROP*						
Fellow eye worse than PT	14	4.3%	14	4.3%	28	4.3%
At least 1 eye zone I†	77	23.7%	75	23.2%	152	23.4%
Stratum B—at least 1 eye PT						
Both eyes zone II PT	167	51.4%	164	50.6%	331	51.0%
1 eye less than PT	67	20.6%	71	21.9%	138	21.3%
Infants with zone I ROP	88	27.1%	91	28.1%	179	27.6%
Infants with zone II ROP	237	72.9%	233	71.9%	470	72.4%
Plus disease infants‡	107	32.9%	112	34.6%	219	33.7%
Non-plus disease infants	218	67.1%	212	65.4%	430	66.3%
Time from first§ PT diagnosis to randomization (infants in category)						
≤24 h	115	35.5%	100	31.6%	215	33.2%
>24, ≤48 h	127	39.2%	128	39.6%	255	39.4%
>48 h	82	25.3%	95	29.4%	177	27.4%
Missing	1		1		2	

* PT indicates prethreshold retinopathy of prematurity.
† Note that in stratum A, infants with bilateral zone I ROP and 1 eye already at threshold or beyond, are categorized as "fellow eye worse than prethreshold."
‡ Plus disease is defined as present when there is posterior pole vascular dilation and tortuosity in at least 2 quadrants. An infant is a plus disease infant if at least 1 study eye has plus disease at baseline. Similarly, an infant is a zone I infant if at least 1 study eye has zone I ROP.
§ "First PT diagnosis" is the date/time of the first examination that showed prethreshold ROP in at least 1 eye that was subsequently confirmed on a second examination.

infants who changed mode of support in 1 direction or the other between nasal cannula and ventilator/CPAP/hood during the first 24 hours after randomization are not included in these calculations.)

Table 4 demonstrates that the distributions of median saturations achieved over the first 2 weeks after randomization were different for the 2 treatment arms. During the first 2 weeks, only 8.0% of median saturations for infants assigned to the conventional arm were in the supplemental range or higher, and

TABLE 4. Distribution of Infants According to Median Pulse Oximetry Over the First Two Weeks on Study

Median Pulse Oximetry Value Over First 2 Weeks, (%)	Conventional Arm* n = 325	Supplemental Arm* n = 324
<89	.0	.0
89	.0 |	.0
90	.3 |	.0
91	16.9 |	.0
92	34.5 |	.3
93	19.1 |	.3
94	14.5 |	1.2
95	6.2	6.8
96	3.7	23.5 |
97	2.8	56.5 |
98	.9	9.6 |
99	.0	.6 |
100	.6	.3
Missing	.6	.9

The | symbols indicate the targeted range of saturation values for each arm of the study.
* Each study arm column gives the percentage of all subjects in that column whose median pulse oximetry over the first 2 weeks on study was at the level shown in the left hand column.

only 1.8% of median saturations of infants assigned to supplemental therapy were in the conventional range or lower. Pulse oximetry was recorded from all enrollees for these first 2 weeks of study participation, but beyond this period, as the eyes reached study endpoints, fewer infants remained on equipment to contribute to the accumulating oximetry data. In addition, as some infants in the conventional arm had resolution of their CLD, their saturations became greater than 95% while breathing room air. Figure 4 shows the smoothed overall frequency distribution of the saturation values (1 reading every 40 seconds) for the full period until ophthalmic endpoints for all infants enrolled. These data also include the 81 conventional and 85 supplemental infants who continued to use study equipment at home. Refusal of the parents or guardians to take the study equipment home on the day of discharge was a primary cause of premature cessation of pulse oximetry and study assigned oxygenation, occurring in 26 conventional and 24 supplemental subjects. Many of these families/guardians were willing to continue returning for weekly follow-up examinations, and therefore, were not withdrawn from the study. Comparison of the SES of families who refused equipment, with those that accepted it at home, showed no relationship between SES and refusal of this major home challenge, nor success in remaining in the target zones at home (data not shown).

Ophthalmic Outcome Data

The primary outcome, the proportion of infants with at least 1 eye progressing to confirmed threshold ROP, is shown by treatment arm in Table 5 for all infants and for subgroups of infants defined by baseline ophthalmic characteristics. Overall, 48.5% (145/299) of infants with study endpoints and assigned to the conventional arm progressed to confirmed threshold ROP in at least 1 eye, compared with 40.9%

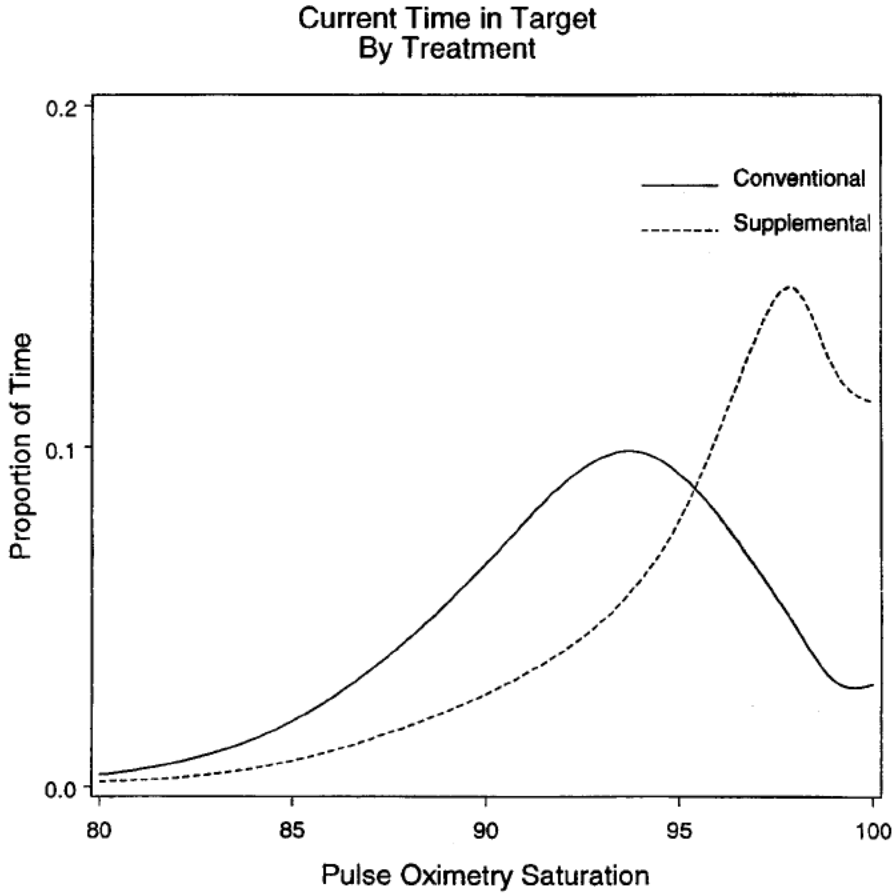

Fig 4. Smoothed frequency distribution of pulse oximetry saturation values for the conventional and supplemental oxygen arms throughout the duration of time on study equipment. Pulse oximetry saturation values were recorded to disk for later analysis once every 40 seconds throughout the time an infant remained on study equipment (range: 2–25 weeks).

TABLE 5. Progression to Threshold ROP* by Ophthalmic Characteristics and Treatment Assignment

Characteristic	Conventional		Supplemental		Total	
	n	%	*n*	%	*n*	%
Enrolled	325	100%	324	100%	649	100%
Without eye endpoints†	26	8%	26	8%	52	8%
With eye endpoints†	299	92%	298	92%	597	92%
Infants with eye endpoints†	299	100%	298	100%	597	100%
Progression to threshold	145	48%	122	41%	267	45%
Stratum A (progressed/total)	46/84	55%	37/81	46%	83/165	50%
Fellow eye worse than PT‡	8/13	62%	8/14	57%	16/27	59%
At least 1 study eye zone I	38/71	54%	29/67	43%	67/138	49%
Stratum B (progressed/total)	99/215	46%	85/217	39%	184/432	43%
Both eyes zone II PT	80/152	53%	66/152	43%	146/304	48%
1 eye less than PT	19/63	30%	19/65	29%	38/128	30%
Infants with zone I ROP, in at least 1 eye	46/82	56%	41/83	49%	87/165	53%
Infants with zone II ROP	99/217	46%	81/215	37%	180/432	42%
Plus disease infants§	54/103	52%	59/103	57%	113/206	55%
Non-plus disease infants§	91/196	46%	63/195	32%	154/391	39%
Time elapsed from randomization‖						
All study eyes						
To adverse outcome, wk	2.4 ± 2.0		2.7 ± 2.0		2.5 ± 2.0	
To favorable if resolved, wk	9.0 ± 3.8		9.5 ± 4.0		9.2 ± 3.9	
Eyes <PT ROP at randomization	14/62 (22.6%)		14/61 (23.0%)		28/123 (22.8%)	
To adverse outcome, wk	1.7 ± 1.1		3.2 ± 1.3		2.4 ± 1.4	
To favorable outcome, wk	7.8 ± 3.8		8.2 ± 3.9		8.0 ± 3.8	
Eyes without plus disease						
To adverse outcome, wk	2.3 ± 2.1		2.7 ± 2.0		2.5 ± 2.1	
To favorable outcome, wk	8.9 ± 4.0		9.5 ± 4.1		9.2 ± 4.1	
Eyes with plus disease						
To adverse outcome, wk	1.6 ± 1.0		2.2 ± 1.9		1.9 ± 1.6	
To favorable outcome, wk	7.5 ± 2.9		7.1 ± 3.3		7.3 ± 3.1	

* Infant ophthalmic outcomes based on progression of at least 1 study eye to threshold ROP. If an infant entered the study with 1 eye already at threshold or worse, that eye was not a study eye, and the infant's outcome is based on only the study eye.
† "Eye endpoints" means that for that infant, the primary endpoint of either 1) at least 1 eye progressing to threshold, or 2) all study eyes not progressing to threshold is known.
‡ PT indicates prethreshold ROP.
§ "Plus disease infants" are those who have at least 2 quadrants of posterior pole dilation/tortuosity in at least 1 study eye, whereas "non-plus disease infants" have all study eyes with 0 or 1 quadrant of posterior pole dilation/tortuosity.
‖ Mean ± standard deviation.

(122/298) in the supplemental arm. The difference between treatment arms was not significant at the designed 1-tailed α-level of .025, as adjusted for sequential testing. However, the difference was still suggestive, with a 1-tailed P value adjusted for repeated interim analyses of .032.[38] When eyes whose outcomes could be assigned by the Ophthalmic Endpoints Committee were included (31 infants: 15 conventional and 16 supplemental), the progression rates remained similar: 46.2% (145/314) and 39.5% (124/314) for the conventional and supplemental arms, respectively (data not shown).

Analysis by stratum or zone of baseline ROP yielded similar results. The high severity ROP stratum A infants progressed to threshold more frequently than the lower risk stratum B infants (50% vs 43% overall). Higher rates of progression in the conventional arm than in the supplemental arm were observed for both ROP severity strata (55%–46% in stratum A and from 46%–39% in stratum B). When severity was alternatively examined by zone of prethreshold ROP, progression rates also were lower in the supplemental arm (56% vs 49% for zone I and 46% vs 37% for zone II; conventional vs supplemental, respectively); however, none of these differences were statistically significant. In contrast, when progression rates were examined in relation to plus disease, the subgroup analysis revealed a difference. Infants without plus disease in either study eye progressed to threshold 46% versus 32% of the time in the conventional and supplemental arms, respectively (P = .004). When at least 2 quadrants of posterior pole dilation/tortuosity were present in either study eye at baseline, 52% of conventional versus 57% of supplemental infants had at least 1 eye progress to threshold (P = .484).

Adverse outcomes occurred soon after randomization in both groups as shown in Fig 5A, and the elapsed time from study entry to adverse ophthalmic endpoints was slightly longer in the supplemental arm compared with the conventional arm. Mean progression time to threshold disease was 2.4 weeks for eyes in the conventional arm and 2.7 weeks for eyes in the supplemental arm. Eyes with plus disease at study entry progressed to threshold disease most rapidly, at a mean of 1.6 and 2.2 weeks in the conventional arm and supplemental arm, respectively. Eyes without plus disease took somewhat longer (mean of 2.3 weeks and 2.7 weeks, respectively; Table 5). Achieving a favorable outcome took longer (Fig 5B), and the time to full vascularization or zone III vessels on 2 consecutive examinations in eyes

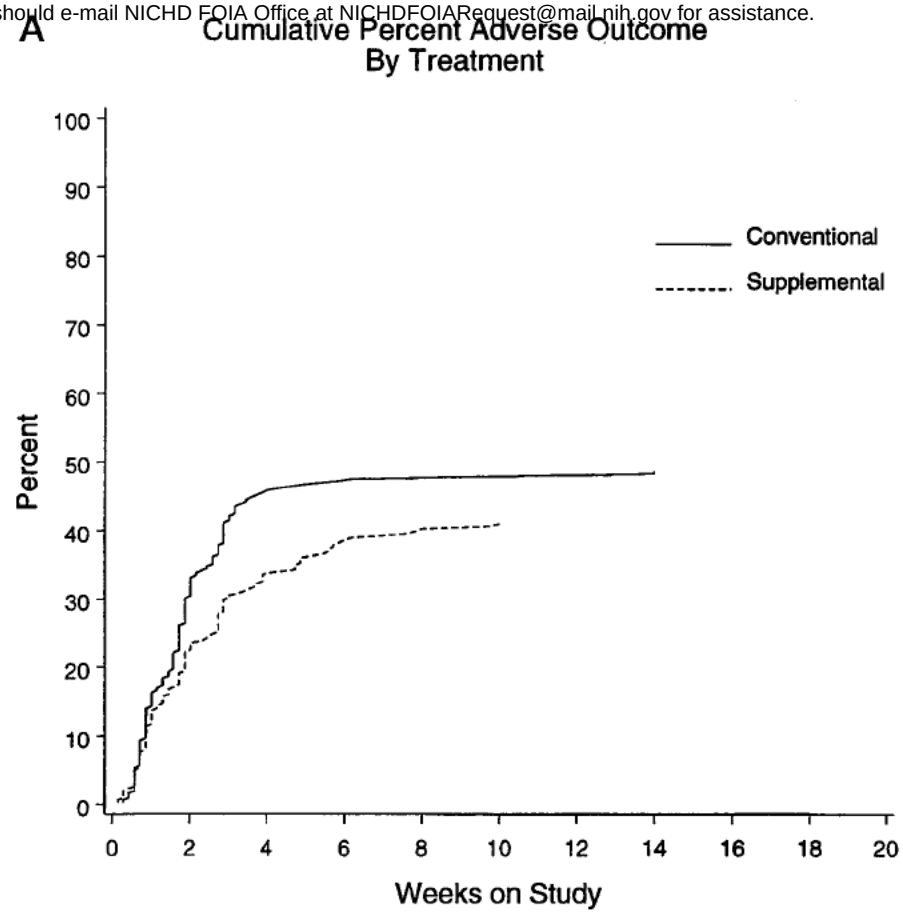

Fig 5. Cumulative rate curves demonstrating the differences in both the proportion and timing of adverse (A) and favorable (B) ophthalmic outcomes by study arm.

without progression to threshold disease occurred in the conventional arm at a mean of 9.0 weeks and in the supplemental arm at a mean of 9.5 weeks. Threshold ROP, when it occurred, was diagnosed at an average PMA of 36.8 weeks (range: 31.6–50.9 weeks) in the conventional arm, and an average of 37.3 weeks' PMA (range: 32.3–45.1 weeks) in the supplemental arm (data not shown in table).

Multiple regression analysis was conducted to adjust for minor variations in baseline characteristics with both simple and complex models. The complex model included treatment assignment, ROP stratum, race, gender, gestational age, small for gestational age status, the baseline pulmonary severity score, plus disease, late versus on-time enrollment, degree of compliance with assigned saturations, interactions of these variables with treatment assignment, and study center. The analysis did not alter the conclusions, but did confirm that both black race (odds ratio [OR]: .44; 95% confidence interval [CI]: .20,.94) and higher gestational age (OR: .80 per week; 95% CI: .66,.98) provide important significant protective effects in reducing the chance of progression of prethreshold ROP to threshold ROP, regardless of treatment arm, while having 2 or more quadrants of posterior pole dilation/tortuosity (plus disease) increased the risk of progression to threshold (OR: 1.71; 95% CI: .95,3.10). In the simplified model, the OR for the supplemental arm after adjustment for ROP risk stratum, plus disease, race, and gestational age was .72 (95% CI: .52,1.01).

Peripheral ablation utilized laser therapy in 93% of treated eyes (73% diode and 20% Argon) and cryotherapy alone in 7%. Four percent of treated eyes received both laser and cryotherapy. Final ophthalmic outcomes based on all study eyes at 3 months' corrected age (or 6 months for 12 conventional and 18 supplemental eyes) revealed adverse outcomes (partial or total retinal detachment, retinal folds, or obstruction of the visual axis) in 4.4% of the study eyes in the conventional and 4.1% in the supplemental arms, and macular ectopia in an additional 3.9% of the study eyes of the conventional arm and 3.9% of the study eyes of the supplemental arm. Among just those eyes that developed threshold ROP and were treated with peripheral surgical ablation, 9.2% in the conventional arm and 13.2% in the supplemental arm had adverse ophthalmic outcomes at 3 to 6 months (excludes macular ectopia that occurred in 6.3% of conventional and 7.7% of supplemental laser/cyro-treated eyes).

Pediatric Outcomes

We hypothesized that infants in the supplemental arm would grow and gain weight faster than infants in the conventional arm, but there were no differences between their growth rates during the initial first 2 weeks, later during the hospitalization period (data not shown), or at 3 months' corrected age (Table 6).

However, markers of CLD severity both during hospitalization and remaining at 3 months' corrected age (50 weeks' PMA) suggest a somewhat worse pulmonary status in the supplemental arm after randomization, although there were no differences in the baseline status measures (Table 2). As shown in Table 6, the conventional arm had fewer infants with 1 or more episodes of pneumonia or CLD exacerbation than did the supplemental arm, 25 (8.5%) versus 38 (13.2%; $P = .066$), and there were also fewer total episodes in the conventional arm (29 vs 51). Using the baseline pulmonary scores to further examine this, infants were divided into higher and lower pulmonary risks at the overall median pulmonary score of .430. The difference in pneumonia/CLD events was confined to the infants with the higher half of the pulmonary scores (10.6% in the conventional arm vs 18.7% in the supplemental arm; $P = .051$) and did not differ among the infants with the lower half of the pulmonary scores (6.5% in the conventional arm vs 6.8% in the supplemental arm; $P = .93$; data not in table). Rehospitalization rates for pulmonary causes (excluding for apnea alone), and death rates from pulmonary causes were similar in the 2 arms (Table 6). However, at the 3-month examination (50 weeks' PMA), more infants in the supplemental arm remained hospitalized (12.7% vs 6.8%; $P = .012$), on oxygen (46.8% vs 37.0%; $P = .020$), and on diuretics (35.8% vs 24.4%; $P = .002$). The proportion of infants who experienced any 1 or more of these adverse pulmonary events by 3 months' corrected age as defined by remaining hospitalized, remaining on study equipment, oxygen, steroids, methylxanthines, or diuretics was significantly higher in the supplemental arm than in the conventional arm (57% vs 46%, respectively; $P = .005$). Regression analysis adjusting for the important baseline covariates of race, ROP severity, gestational age, and pulmonary status did not change the significance of these findings.

Adverse events from sepsis without pneumonia did not differ between the 2 arms, and survival through the 3-month examination was similar (97.8% conventional vs 97.2% supplemental). Mean PMA at discharge for those infants going home was the same in both arms at 41 ± 3 weeks (range: 35–56), and infants in both arms were able to take oral feeds without a gastric tube at the mean PMA of 39 weeks. At the 3-month follow-up examination, developmental levels as assessed by the Revised Parental Denver Questionnaire were similar (equivalent ages = 3.5 ± 1.4 months in the conventional arm vs 3.4 ± 1.4 months in the supplemental arm).

DISCUSSION

These findings demonstrate that supplemental oxygen, as used in this study for prethreshold ROP, did not significantly decrease the proportion of infants who have at least 1 eye progress to threshold ROP, although the differences were close to nominal statistical significance. Using the observed conventional progression rate of 48%, the study has a power of 70% against a 10-percentage point absolute difference, and a power of 98% against a one third reduction, adjusting for the use of repeated interim analyses as described above. The resultant power is lower than expected because the adverse ophthalmic outcome rate in the conventional group was higher than expected.

TABLE 6. Pediatric Outcomes Between Randomization and Three Months' Corrected Age*

	Conventional n = 325	Supplemental n = 324
Event occurring after randomization		
Weight gain over the first 2 wk (g; mean ± standard deviation)	291 ± 137	278 ± 143
Length gain over the first 2 wk (cm; mean ± standard deviation)	1.8 ± 1.8	1.7 ± 2.0
Head circumference increase the 1st 2 wk (cm; mean ± standard deviation)	1.6 ± 1.0	1.4 ± .9
PMA at discharge home† (wk; mean ± standard deviation)	41.1 ± 3.3	41.3 ± 3.4
PMA to achieve oral feeding‡ (wk; mean ± standard deviation)	39.0 ± 3.5	38.9 ± 3.6
Infants with pneumonia/CLD events (total # of events)§	25 (29)	38 (51)
Infants with sepsis, but no pneumonia/CLD (total # events)	12 (12)	11 (11)
Infants with apnea/bradys triple baseline (total # events)	26 (36)	30 (33)
Outcomes at the 3-month corrected age window‖		
Remained hospitalized¶ (%)	6.8%	12.7%
Remained on study equipment (%)	3.1%	3.4%
Remained on oxygen (%)	37.3%	46.8%
Remained on steroids (%)	12.5%	14.2%
Remained on methylxanthines (%)	13.5%	14.7%
Remained on diuretics (%)	24.4%	35.8%
Infants with any 1 of the above, # of infants (%)#	148 (45.5%)	183 (56.5%)
Outcomes at 3 months' corrected age examination	n = 301	n = 302
Infants rehospitalized (# of all rehospitalizations)	99 (132)	87 (116)
Infants rehospitalized for pulmonary reasons, not apnea (# of all rehospitalizations)	46 (53)	41 (49)
All deaths, n (pulmonary cause of death, n)	7 (3)	9 (5)
Room air saturations too low to test, n (%)	17 (6%)	35 (12%)
Room air oxygen saturation for those tested, mean ± standard deviation	95.3 ± 4.7%	94.6 ± 7.7%
Weight gain from randomization (mean ± standard deviation; kg)	2.96 ± 1.00	2.88 ± 1.05
R-PDQ developmental level** (mean ± standard deviation; mo)	3.5 ± 1.4	3.4 ± 1.4

* Corrected age indicates months after the date an infant should have been born at full term (3 months' corrected = 52 weeks' PMA).
† Limited to infants who were discharged to home (ie, excludes deaths, loss to follow-up, and those remaining hospitalized at the 3-month examination).
‡ Excludes 16 conventional and 33 supplemental infants who were not yet feeding by mouth by 50 weeks' PMA, 2 conventional and 7 supplemental infants who died before oral feeds, and 6 conventional and 7 supplemental infants with incomplete data. Oral feeds means that the infant was taking all enteral feedings by nipple (bottle or breast).
§ Excludes 30 conventional and 36 supplemental infants recruited early in the trial for whom these data were not collected.
‖ The 3-month corrected age window was a target of 12 ± 2 weeks after due date, or 50 to 54 weeks' PMA. Outcomes are reported as of 50 weeks' PMA to permit comparisons as some infants were examined late in the window or outside this window.
¶ Values exclude 31 infants with missing data at 50 weeks' PMA attributable to loss to follow-up (14 conventional and 17 supplemental).
# Number of infants, and percent of all enrollees represented by any 1 or more of the 3-month events.
** R-PDQ indicates the Revised Parental Denver Questionnaire.[26]

In STOP-ROP, the observed rate of progression from prethreshold to threshold (48%) in the conventional arm is higher than reported in the CRYO-ROP study (33%) for a number of reasons that can be identified. The eligibility criteria for STOP-ROP excluded nearly half of the infants who would have been included in the CRYO-ROP study, and these were the ones that did not require oxygen and had less severe lung disease at the time of prethreshold ROP. The STOP-ROP enrollees had lower birth weights than the CRYO-ROP infants (726 g in STOP-ROP vs ~850 g for CRYO-ROP prethreshold).[1] During the CRYO-ROP study, borderline threshold cases were judged as not threshold, to avoid treating eyes with an unproven intervention. Because peripheral ablation has been demonstrated to be effective for threshold ROP, this is no longer true, and as in clinical practice, the STOP-ROP study judged in favor of the diagnosis of threshold disease in borderline cases. Finally, the differences in the STOP-ROP definition of threshold ROP in zone I (see Table 1) would result in more infants being diagnosed with threshold ROP during the STOP-ROP trial.

The STOP-ROP results differ from the 2 smaller case series in the literature in which supplemental oxygen for infants with prethreshold ROP was associated with a high regression rate of prethreshold ROP without the need for ablative retinal surgery.[28,29] Some of the possible explanations are differences in patient selection, level of oxygen administration, timing of the intervention, and use of historical controls in the case series. Infants in these case series may have had milder ROP than those enrolled in STOP-ROP, and the effect of that would be higher progression rates in STOP-ROP. The average birth weight of the infants in that series was 814 g, heavier than the 726-g average birth weight of infants enrolled in STOP-ROP, and therefore, at lower risk for severe ROP. In the Gaynon et al[28] series, if infants were mostly detected as having pretheshold ROP before developing plus disease, the findings in that series and the subgroup of infants in STOP-ROP without plus disease would be more consistent. Large differences in reported improvements between historically controlled case series and randomized trials are well recognized and are usually attributed to changes in several aspects of medical care over time, as well as patient selection. STOP-ROP expended considerable effort to maximize the time infants were in their targeted ranges of saturation and not at saturation levels of 100%. In contrast, however, the saturation targets were "a minimum of 99%" in the Gaynon et al study,[28] and "a minimum of 98%" in the Seiberth et

al report.[38] Thus, infants in those 2 series probably had higher average saturation levels than the STOP-ROP supplemental group. To compare the target range of the supplemental arm in STOP-ROP as measured by the Ohmeda 3740 oximeter with these other 2 studies, it could be argued that 1.6 saturation points should be added to the STOP-ROP range to make the saturation monitor readings equivalent. If this is done, the STOP-ROP supplemental range becomes 97.6% to 100% saturation, even closer to the reported series and, therefore, not an explanation of differences.

Another alternative explanation may be in the timing of treatment. If immediate application of the supplemental oxygen at prethreshold diagnosis would provide maximum benefit, it could be argued that use in standard practice would result in earlier and possibly more effective treatment of eyes with prethreshold ROP. Gaynon reports (D. L. Phelps, personal communication, October 1999) that ROP screening was performed at weekly intervals in their series, which could be expected to reduce the number of infants reaching plus disease before beginning oxygen treatment. Screening examinations before prethreshold identification were usually performed every 2 weeks in the STOP-ROP centers, consistent with the AAP recommendations. In addition, the process of obtaining both an independent confirming examination and informed consent of the family or guardians resulted in delays between the first time that prethreshold ROP was observed and the start of the study intervention. In approximately one quarter of the cases, this was >48 hours.

Oxygen requirements go up by ~5 to 9 percentage points when changing to supplemental oxygen from the conventional range, emphasizing that infants truly receive more oxygen when assigned to the supplemental arm. We had not expected that pulmonary events of pneumonia and/or CLD exacerbations were going to be 1.8 times more likely to occur in the supplemental arm. The absolute increase in acute pulmonary events of 7.3% gives a number-needed-to-treat calculation of 1 more pneumonia/CLD episode for each 13.7 infants treated with supplemental oxygen. The ROP progression data give a number-needed-to-treat of 13.2 infants to prevent 1 case of progression to threshold ROP. By this analysis, one could expect ~1 episode of pneumonia/CLD exacerbation for each case of peripheral ablative surgery that might be prevented. That might be regarded as a reasonable trade-off by most neonatologists and ophthalmologists, but the condition of the infants at 3 months' corrected age must also be considered. At that time, 97% of subjects were off the study assigned treatments, and those in the supplemental arm continued to need more oxygen and diuretics, and a greater number remained hospitalized. Our data suggest that the magnitude of any benefit from supplemental oxygen in reducing the need for surgery is likely to be on the order of 7% to 14%, with no reduction in the number of retinal detachments. The potential long-term advantage of avoiding peripheral ablative surgery for ROP is unknown, but to the extent long-term side effects might occur, even a small reduction in surgery rates may be of value. The potential long-term effects, both of costs and to the families, of prolonging hospitalization from worsened lung disease also should be considered.

Our original hypothesis was not only that supplemental oxygen would prove beneficial for the eyes of infants with prethreshold ROP whose pulse oximetry in room air is <94%, but in addition, that it would be beneficial for CLD, resulting in better growth and lower pulmonary vascular resistance.[39,40] However, Supplemental oxygen at a target range of 96% to 99% saturation seemed to have deleterious effects on CLD in some infants, with no change in growth or neuromotor development. Previous reports of an improvement in weight gain and resolution of cor pulmonale with oxygen supplementation could be explained if saturation levels in the control infants of those studies were even lower than the STOP-ROP conventional range. This is certainly possible, because those reports date from periods preceding the routine availability of continuous pulse oximetry. Fortunately, others are investigating this question in a carefully controlled randomized trial in Australia. The Benefits of Oxygen Saturation Targeting Trial is currently enrolling infants in a test of the safety and efficacy of supplemental oxygen for infants with CLD. ROP is not an entry criterion in that study, but will be examined as a secondary outcome (D. Henderson-Smart, personal communication, 1999).

These results provide valuable data for the clinician. The STOP-ROP data clearly demonstrate that oxygen, at saturation levels of 96% to 99% does not increase the severity of ROP in the eyes of infants with prethreshold ROP, even in the 123 eyes with ROP of less than pretheshold severity at randomization. There are no data, however, to suggest that the higher saturation levels are safe for the early immature eye that does not yet have established ROP. The reported data apply only to infants who are well beyond the initial weeks after birth and must not be interpreted as showing safety of supplemental levels of oxygen at younger ages.

The present study does not rule out a potential small reduction in the rate of ROP progression with supplemental oxygen, and a subgroup analysis suggests that supplemental oxygen, as used in this study, may be more effective in pretheshold ROP without plus disease. However, secondary analyses, not prespecified, must be cautiously interpreted and require additional study. The predictive value of various possible definitions of prethreshold ROP have not been systematically studied and reported but could prove very important and should be investigated. The data show a modest deleterious effect of supplemental oxygen on CLD in some infants with more severe lung disease at baseline. Therefore, clinicians must consider which patients might tolerate the added pulmonary risk of supplemental oxygen as a therapeutic intervention for their ROP. If an infant requires saturations of 96% to 99% for cardiopulmonary reasons, fear about causing worse ROP is not a reason to withhold the oxygen. Results from other studies, such as the Benefits of Oxygen Satura-

tion Targeting Trial, may help further our understanding of the effects of supplemental oxygen in infants with CLD.

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Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), A Randomized, Controlled Trial. I: Primary Outcomes

The STOP-ROP Multicenter Study Group

Pediatrics 2000;105;295-310
DOI: 10.1542/peds.105.2.295

From: Michael O`Shea
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Cc: Robert Dillard
Subject: RE: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)
Date: Wednesday, November 30, 2005 1:54:57 PM

Neil and Rose,

Sorry I missed the call - I'm in the NICU this week. Bob Dillard and I discussed Neil's proposed changes in response to the DSMC concerns and agree with what he's proposed.

Thank you,

Mike

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 29, 2005 7:44 PM
To: Petrie, Carolyn; wrich@ucsd.edu; Hastings, Betty J.; Zaterka-Baxter, Kristin; Alice.J.Reardon@uth.tmc.edu; nirupama_laroia@urmc.rochester.edu; Walid.Salhab@UTsouthwestern.edu; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; D'Angio, Carl; Brenda Poindexter; Brenda.H.Morris@uth.tmc.edu; Krisa Van Meurs; Gantz, Marie; Poole, W. Kenneth; [SCRN] Stoll, Barbara; Charles.Rosenfeld@UTSouthwestern.edu; dale_phelps@urmc.rochester.edu; Das, Abhik; dstevenson@stanford.edu; edward.donovan@chmcc.org; goldb008@mc.duke.edu; jlemons@iupui.edu; Jobea0@chmcc.org; jon.e.tyson@uth.tmc.edu; alaptook@WIHRI.org; mcw3@cwru.edu; Michael O`Shea; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; sduara@miami.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; WOh@wihri.org; D'Angio, Carl; ambal@sprynet.com
Cc: aellison@med.miami.edu; echaisso@iupui.edu; bvecchio@careNE.org; (b) (6); debra.camputaro@yale.edu; diane.timmer@cchmc.org; fmartinez@ucsd.edu; Karen.Kirby@UTSouthwestern.edu; Ktownsen@med.wayne.edu; KGilley@CareNE.org; lisa.joo@stanford.edu; msumner@peds.uab.edu; [SCRN] Tinsley, Mazie; [SCRN] Dunbar-Scott, Renee; Jensen, Rosemary; gonza025@mc.duke.edu; Wendy D. Holcomb
Subject: RE: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)

Hi
For the morning call, I have attached the response from Neil Finer and the SUPPORT Subcommittee. Please read this over before the call if time permits. Also attached is a late breaker abstract from PAS looking at saturation data in premature infants. If you are unable to make the call, please insure that your alternate PI or another representative for your site is on the call. This is CRUCIAL for input and a DSMC response.

Thanks for all your help.

Rose

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Tue 11/29/2005 4:55 PM
To: Petrie, Carolyn; wrich@ucsd.edu; Hastings, Betty J.; Zaterka-Baxter, Kristin; Alice.J.Reardon@uth.tmc.edu; nirupama_laroia@urmc.rochester.edu; Walid.Salhab@UTsouthwestern.edu; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; D'Angio, Carl; Brenda Poindexter; Brenda.H.Morris@uth.tmc.edu; Krisa Van Meurs; Gantz, Marie; Poole, W. Kenneth; [SCRN] Stoll, Barbara; Charles.Rosenfeld@UTSouthwestern.edu; dale_phelps@urmc.rochester.edu; Das, Abhik; dstevenson@stanford.edu; edward.donovan@chmcc.org; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD); jlemons@iupui.edu; Jobea0@chmcc.org; jon.e.tyson@uth.tmc.edu; alaptook@WIHRI.org; mcw3@cwru.edu; moshea@wfubmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; sduara@miami.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; WOh@wihri.org; D'Angio, Carl; ambal@sprynet.com
Cc: aellison@med.miami.edu; echaisso@iupui.edu; bvecchio@careNE.org; (b) (6); debra.camputaro@yale.edu; diane.timmer@cchmc.org; fmartinez@ucsd.edu; Karen.Kirby@UTSouthwestern.edu; Ktownsen@med.wayne.edu; KGilley@CareNE.org; lisa.joo@stanford.edu; msumner@peds.uab.edu; [SCRN] Tinsley, Mazie; [SCRN] Dunbar-Scott, Renee; Jensen, Rosemary; gonza025@mc.duke.edu; Wendy Holcomb
Subject: RE: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)

Reminder for tomorrow's call:

The NRN conference call to discuss potential strategies to resume the SUPPORT Trial is scheduled for

Wednesday, November 30th

9:30-10:30am ET (6:30-7:30am PT)

To join the call,

Dial Toll Free, 866-675-(b) (6)

Passcode:(b) (6)

PIs: Please ensure that every center is represented for this call.

Carolyn Petrie Huitema

Neonatal Research Network Coordinator

RTI International

6110 Executive Blvd

Suite 902

Rockville, MD 20852

ph. (301) 230-4648

fx. (301) 230-4646

From: Michele Walsh
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Response to DSMC Steering Nov 30 05
Date: Wednesday, November 30, 2005 1:34:04 PM
Attachments: Response to DSMC Steering Nov 30 05MW comment.doc

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Thanks for this excellent work Neil. I spent some time making editorial changes that I believe will facilitate the DSMCs review of this comprehensive and complex document.
(I guess I am still in book editor mode!) Hope this helps.
Michele
----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
To: <alaptook@WIHRI.org>; "Abhik Das" <adas@rti.org>; "Brenda Poindexter" <bpoindex@iupui.edu>; "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>; "Charles Rosenfeld" <crosen@mednet.swmed.edu>; "Dale Phelps" <dale_phelps@urmc.rochester.edu>; "Ed Donovan" <edward.donovan@cchmc.org>; "Ehrenkranz Richard (E-mail)" <richard.ehrenkranz@yale.edu>; "Jobe Alan (E-mail)" <Jobea0@chmcc.org>; "Lemons Jim (E-mail)" <jlemons@iupui.edu>; "Michael O'Shea" <moshea@wfubmc.edu>; "Michelle Walsh" <mcw3@po.cwru.edu>; "Neil Finer" <nfiner@ucsd.edu>; "Oh William (E-mail)" <william_oh@brown.edu>; "Poole Kenneth (E-mail)" <poo@rti.org>; "Ronald GOldberg" <goldb008@mc.duke.edu>; "Shahnaz Duara" <sduara@miami.edu>; "Shankaran Seetha (E-mail)" <s_shankaran@wayne.edu>; "Stevenson David (E-mail)" <dstevenson@stanford.edu>; "Stoll Barbara (E-mail)" <barbara_stoll@oz.ped.emory.edu>; "Tyson Jon (E-mail)" <Jon.E.Tyson@uth.tmc.edu>; <walid.salhab@utsouthwestern.edu>
Cc: "D'Angio, Carl" <Carl_Dangio@URMC.Rochester.edu>; "Laroia, Nirupama" <Nirupama_Laroia@URMC.Rochester.edu>; <vanmeurs@stanford.edu>; "Avroy A. Fanaroff" <aaf2@case.edu>; <reverett@med.miami.edu>; <kurt.schibler@cchmc.org>; <ambal@uab.edu>; "Morris, Brenda H" <Brenda.H.Morris@uth.tmc.edu>; "Michael Cotten" <cotte010@mc.duke.edu>; "Wade Rich" <wrich@ucsd.edu>; "Gantz, Marie" <mgantz@rti.org>; "Petrie, Carolyn" <petrie@rti.org>
Sent: Wednesday, November 30, 2005 11:22 AM
Subject: Response to DSMC Steering Nov 30 05

HI,
Attached is the final response to the DSMC as discussed on the phone this morning. Please review this and let me know by tomorrow (December 1) evening if this is acceptable to you and your site.
A special thanks to Neil and RTI (Marie and Abhik) for all the time and effort that has been put into this project!!
Rose
<<Response to DSMC Steering Nov 30 05.doc>>

In response to the comments and concerns of the DSMC, the SUPPORT committee held a conference call Monday Nov 28th at 10:00 to 1130AM to prepare a response.

- The DSMC made the following 2 comments in their letter regarding the SUPPORT trial. This was generated after they reviewed the oximeter data, which was corrected back to actual SpO2 values from the altered values displayed at the bedside:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

We have responded to each of these concerns and our responses are detailed below

Response to Issue Number 1

We appreciate the concern expressed by the DSMC regarding a potential safety issue secondary to durations of SpO2 values > 95%.

1. To date there are no prospective data which define the SpO2s experienced by the ELBW infant from birth as part of usual clinical care. Because no published studies have evaluated the effects of different target SpO2 ranges on important outcomes, this was one of the principle reasons for the design and conduct of the SUPPORT trial.

2. A number of studies have evaluated different alarm limits, but have not reported the actual durations of SpO2 in the various ranges. Nghiem et al in a PAS abstract this year reported that nurses caring for ELBW infants believe that an acceptable oxygen saturation range should include higher upper limits than specified by current policy (Nghiem et al, Nursing Opinions and Practices of Oxygenation in Prematures: The NOPOP Study PAS #3415, 2005). The study by Hagadorn reported as a late breaker at the PAS this year (Hagadorn et al, Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation. PAS 2005, Attached) did report on the experience of monitoring the actual SpO2 for 72 hours in the first 4 weeks of life in 72 ELBW infants. They reported that the "lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for a median of 70 hours (25th-75th percentiles 67-71 hr) during each week. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25th-75th percentiles 91-97%; range of study center medians 91-96%). Centers ranged between 16-71% compliance with their individual intended SpO2 range. Most noncompliance was above intended range." In comparing the SUPPORT data

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evaluated to date by the DSMC, it is of interest that the mean SpO2 in the 2 Oximeter arms is 90% and 92%, with medians of 92% and 94%, all of which are below that reported by Hagadorn et al (median=95).

The 2 other relevant trials, STOP-ROP and BOOST, both enrolled infants at about 32 weeks PCA, and maintained 2 levels of SpO2, 89% to 94% and 91-94% versus 95% to 98% and 96% to 99%, by administration of oxygen. These studies achieved reasonable separation, but did demonstrate substantial overlap of the intended ranges. It is important to note that these studies were testing two ranges both of which were higher than the lower range of the SUPPORT trial (85% to 89%) and were treating infants who, for the most part, had recovered from their acute disease. In the BOOST trial 70% of the enrolled infants were < 28 weeks of age at birth (all of SUPPORT is < 28 weeks), 32 weeks postmenstrual age (PMA), and required oxygen at enrollment (Askie et al, New England Journal of Medicine. 2003; 349(10):959-967). The STOP-ROP trial enrolled infants with pre-threshold ROP at a PMA of 35.4 + 2.5 weeks of age (Phelps et al, Pediatrics. 2000; 105(2):295-310). These trials then gave the higher SpO2 range infants additional oxygen to increase their SpO2 to the desired range. STOP-ROP reported that the infants in the high range had an SpO2 > 95% for > 97% of the monitored time. These studies found an overall increase in pulmonary morbidity in the higher SpO2 range infants.

Examination of oximeter data from one ~~if~~ of the NRN sites (Case Western, Walsh et al) obtained for an ongoing study evaluating infants similar to those enrolled in SUPPORT, and managed with conventional oximeters revealed that for the 9 infants for whom results were available that the percentage of time with ~~and~~ SpO2 > 95% was > 50%.

3. Impact of SUPPORT oximeters algorithm on sat values:

———The oximetry algorithm that was designed for the SUPPORT trial is such that re-conversion of the altered oximeter values does not result in a discrete SpO2 number for every displayed value. SpO2 values, of 93%, 94% 95% and 96% will all be reconverted to a single value in one arm, while 84%, 85%, 86% and 87% will be reconverted to a single value in the other arm. This is a result of having the displayed values return to non-skewed SpO2 values at < 84% and > 96%, a safety design felt to be important by all involved in this trial (See Attached file USCD1). Thus the percentages reported to the DSMC for some of the ranges that include these values were not an accurate representation of the true values. However all values > 96% and < 84% are actual and do not require any conversion.

Percent of time of spent at SpO2 < 84% and > 96%
(RTI, Nov 29, 2005, 14:00 Hrs)

Range	High target (91-95)	Low target (85-89)
< 84%	8.51	16.62
> 96%	22.69	13.60

In the current SUPPORT study, an initial analysis utilizing only unaltered SpO2 values, ~~as shown above , ie~~ those below 84% and above 96%, have shown that one arm had an SpO2 > 96% for 13.6% versus 22.69% of the time for the comparison arm, and the durations of an SpO2 < 84% was also different at 16.62% versus 8.51%. The previously reported value of 36% duration of an SpO2 > 95% for one group represented an artifact of the conversion algorithm as described above. **The values for SpO2s > 96% using ~~unaltered~~ uncorrected data suggests that the SUPPORT trial to date has, if anything, reduced the duration of hyperoxia~~.~~, compared to that experienced by comparable neonates outside the trial.**

In addition, analyses using ~~these values which represent~~ only actual SpO2 values, ~~we can state that the~~demonstrate that infants in this trial are spending approximately 70% of the time with a true SpO2 value between 84% and 96%. We believe that this is information is very encouraging, and suggests that if we are able to further improve adherence to the target ranges that we will achieve an adequate separation between the groups.

4. Impact of inclusion of data from periods in room air on saturation distributions: As part of the SUPPORT trial, we collect information about inhaled oxygen concentration 3 times a day for the first 14 days and daily thereafter. We believe that a more frequent documentation of inhaled oxygen will allow us to determine the actual duration of oxygen exposure. At the present an infant is considered to be receiving supplemental oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized as receiving supplemental oxygen for significant periods when they are actually in room air. This would result in durations of SpO2 greater than 95% that were felt to be modifiable and reported as such when in fact there is no effective treatment for such elevated SpO2s. In addition, we do not know if such SpO2s on room air are associated with any morbidity. From the SUPPORT study data analyses to date we know that infants in room air have SpO2s > 95% for 46% to 69% of the time.

In view of this design, we would suggest that all future analyses for the DSMC evaluate the saturation ranges of <84% and >96% in children on oxygen therapy as those ranges that are outside the target range. ~~considered to be low and high.~~

We believe that the SUPPORT trial will actually define the periods of time that ELBW infants spend with different ranges of SpO2, and that it is essential to collect this information. In addition, as our findings indicate a lower true percent of the time at SpO2 values >95%, and lower median SpO2 values than has previously been reported, we are in fact, reducing the time with high SpO2 values compared to usual care. The SUPPORT trial carefully evaluates risks, and we will be evaluating group differences for all important short and long term outcomes.

The SUPPORT trial methodology actively encourages all caretakers to keep SpO2 < 96% by having alarm limits set at 85% to 95%. These limits were utilized because it was felt that these represented current practice. The oximetry algorithms were designed to keep infants in the narrower target range of 88% to 92% with the realization that setting alarm limits at these values would severely

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increase the frequency of the alarms sounding. Nevertheless, our results to date suggest that we have decreased the expected percent of time > 95%, and in one group the value of 14% may be as low as is achievable in an actual clinical environment.

We believe that the SUPPORT study will define the durations of high and low SpO2 and will be able to determine if there is a threshold duration of either value that is associated with altered outcomes, and for this reason alone, the SUPPORT trial will be very valuable. All of the procedures outlined below in response to your second concern will also allow us to further increase the percentage of time that the infants are in the maximally altered SpO2 ranges which we believe will further increase separation of these groups.

Response to Issue Number 2

There is concern that we have not achieved adequate separation by the current oximeters and study personnel.

1. As described above, ~~Reviewing~~ the newest analyses ~~available as described above, there are~~ show differences in the durations of low and high SpO2s between the 2 oximeter groups. ~~In addition, A~~a careful analysis of the most recent converted values demonstrates that the cumulative time spent with an SpO2 of 90% or less is 24.3% versus 43%, for the 2 oximeter groups, supporting the ability of the altered oximeters to produce differential SpO2 exposures.

2. We do acknowledge that it would desirable to increase the percentage of time in the narrower target range and towards this end would propose the following changes to SUPPORT:

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~~A~~1. We will require **documentation that the alarm limits are set and functional as per protocol every 4-6 hours**. We have found that in some units the high alarms are being defeated, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned to the respiratory therapists, and this procedure is already being done in ~~many~~ some NRN units.

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~~B~~2. We will immediately initiate a **change in our data collection for FiO2 to ensure that DSMC reports more accurately reflect saturations measured while on oxygen therapy and exclude saturations of infants in room air**. We will change the data form to indicate that the infant was either in oxygen for the entire 24 hours, and if not, will check off the actual hours of oxygen exposure, and we will continue with this from of data collection for the entire time that the infant is receiving oxygen. In the current protocol we collect such information 3 times a day for the first 14 days only and then daily thereafter. We believe that more frequent documentation will allow us to determine the actual time that an infant is in room air. At the present the infant is considered in oxygen if he/she requires oxygen for greater than intermittent use. This results in infants being

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categorized in oxygen for significant periods when they are in room air. While in room air, we cannot manipulate the SpO2, and thus knowledge of the true time in oxygen will produce a more accurate representation of oximetry results that are subject to care interventions.

~~3~~C.~~.~~ We will initiate **further training and in-service at all the sites to stress the importance of keeping the SpO2 alarm functional and at the limits of 85% and 95%.** In the past these were guidelines, and we will now change the study manual and protocol to indicate these limits are now set by protocol and that violations will be documented. We will encourage all caretakers to aim for an SpO2 value of 90% and make every effort to educate caretakers to make smaller adjustments in FiO2 and ensure that the infant is maintained between the 87% to 93%, the range with the maximal separation of the study oximeters. We will further facilitate the use of the 2 hour and 12 hour histograms showing the infants' actual ranges to provide feedback to the caretakers regarding the percentage of time in the target ranges.

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D.4. We will **develop guidelines for managing desaturations such that the increase in oxygen is proportional to the severity of the desaturation**. More modulated increases in oxygen during these desaturation events will minimize overshoot and the potential of high SpO2 values.~~We would hope that such changes – ie increasing the FiO2 in steps of 5% as opposed to much larger increases will decrease the resultant overshoots creating the high SpO2 values~~. This will be included in the revised manual of operations.

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5. **We will place bedside cards to indicate the target range.**

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6. We will **initiate compliance monitoring visits coordinated by RTI** to visit random sites. These visits had been planned, but had not yet been initiated. The teams will consist of a member of RTI and a study coordinator, and they will review the adherence to the protocol and any other relevant issues.

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We thank the DSMC for their thoughtful concerns. We trust that our plans to move forward with the SUPPORT trial are acceptable to the DSMC. We are anxious to initiate the above changes, seek IRB approvals and re-activate this trial.

From: Neil Finer

To: Higgins, Rosemary (NIH/NICHD) [E]; "Petrie, Carolyn"; wrich@ucsd.edu; "Hastings, Betty J."; "Zaterka-Baxter, Kristin"; Alice.J.Reardon@uth.tmc.edu; nirupama_laroia@urmc.rochester.edu; Walid.Salhab@UTsouthwestern.edu; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; "D"Angio, Carl"; "Brenda Poindexter"; Brenda.H.Morris@uth.tmc.edu; "Krisa Van Meurs"; "Gantz, Marie"; "Poole, W. Kenneth"; "[SCRN] Stoll, Barbara"; Charles.Rosenfeld@UTsouthwestern.edu; dale_phelps@urmc.rochester.edu; "Das, Abhik"; dstevenson@stanford.edu; edward.donovan@chmcc.org; goldb008@mc.duke.edu; jlemons@iupui.edu; Jobea0@chmcc.org; jon.e.tyson@uth.tmc.edu; alaptook@WIHRI.org; mcw3@cwru.edu; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu; "sduara@miami.edu"; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; WOh@WIHRI.org; "D"Angio, Carl"; ambal@sprynet.com

Cc: aellison@med.miami.edu; echaisso@iupui.edu; bvecchio@careNE.org; (b) (6) debra.camputaro@yale.edu; diane.timmer@cchmc.org; fmartinez@ucsd.edu; Karen.Kirby@UTsouthwestern.edu; Ktownsen@med.wayne.edu; KGilley@careNE.org; lisa.joo@stanford.edu; msumner@peds.uab.edu; "[SCRN] Tinsley, Mazie"; "[SCRN] Dunbar-Scott, Renee"; "Jensen, Rosemary"; gonza025@mc.duke.edu; "Wendy Holcomb"

Subject: RE: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)

Date: Wednesday, November 30, 2005 10:05:20 AM

Attachments: ucsd1.doc

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 29, 2005 4:44 PM
To: Petrie, Carolyn; wrich@ucsd.edu; Hastings, Betty J.; Zaterka-Baxter, Kristin; Alice.J.Reardon@uth.tmc.edu; nirupama_laroia@urmc.rochester.edu; Walid.Salhab@UTsouthwestern.edu; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; D'Angio, Carl; Brenda Poindexter; Brenda.H.Morris@uth.tmc.edu; Krisa Van Meurs; Gantz, Marie; Poole, W. Kenneth; [SCRN] Stoll, Barbara; Charles.Rosenfeld@UTsouthwestern.edu; dale_phelps@urmc.rochester.edu; Das, Abhik; dstevenson@stanford.edu; edward.donovan@chmcc.org; goldb008@mc.duke.edu; jlemons@iupui.edu; Jobea0@chmcc.org; jon.e.tyson@uth.tmc.edu; alaptook@WIHRI.org; mcw3@cwru.edu; moshea@wfubmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; sduara@miami.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; WOh@WIHRI.org; D'Angio, Carl; ambal@sprynet.com
Cc: aellison@med.miami.edu; echaisso@iupui.edu; bvecchio@careNE.org; (b) (6); debra.camputaro@yale.edu; diane.timmer@cchmc.org; fmartinez@ucsd.edu; Karen.Kirby@UTsouthwestern.edu; Ktownsen@med.wayne.edu; KGilley@careNE.org; lisa.joo@stanford.edu; msumner@peds.uab.edu; [SCRN] Tinsley, Mazie; [SCRN] Dunbar-Scott, Renee; Jensen, Rosemary; gonza025@mc.duke.edu; Wendy Holcomb
Subject: RE: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)

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Thanks for all your help.

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Passcode: (b) (6)

PIs: Please ensure that every center is represented for this call.

Carolyn Petrie Huitema

Neonatal Research Network Coordinator

RTI International

6110 Executive Blvd

Suite 902

Rockville, MD 20852

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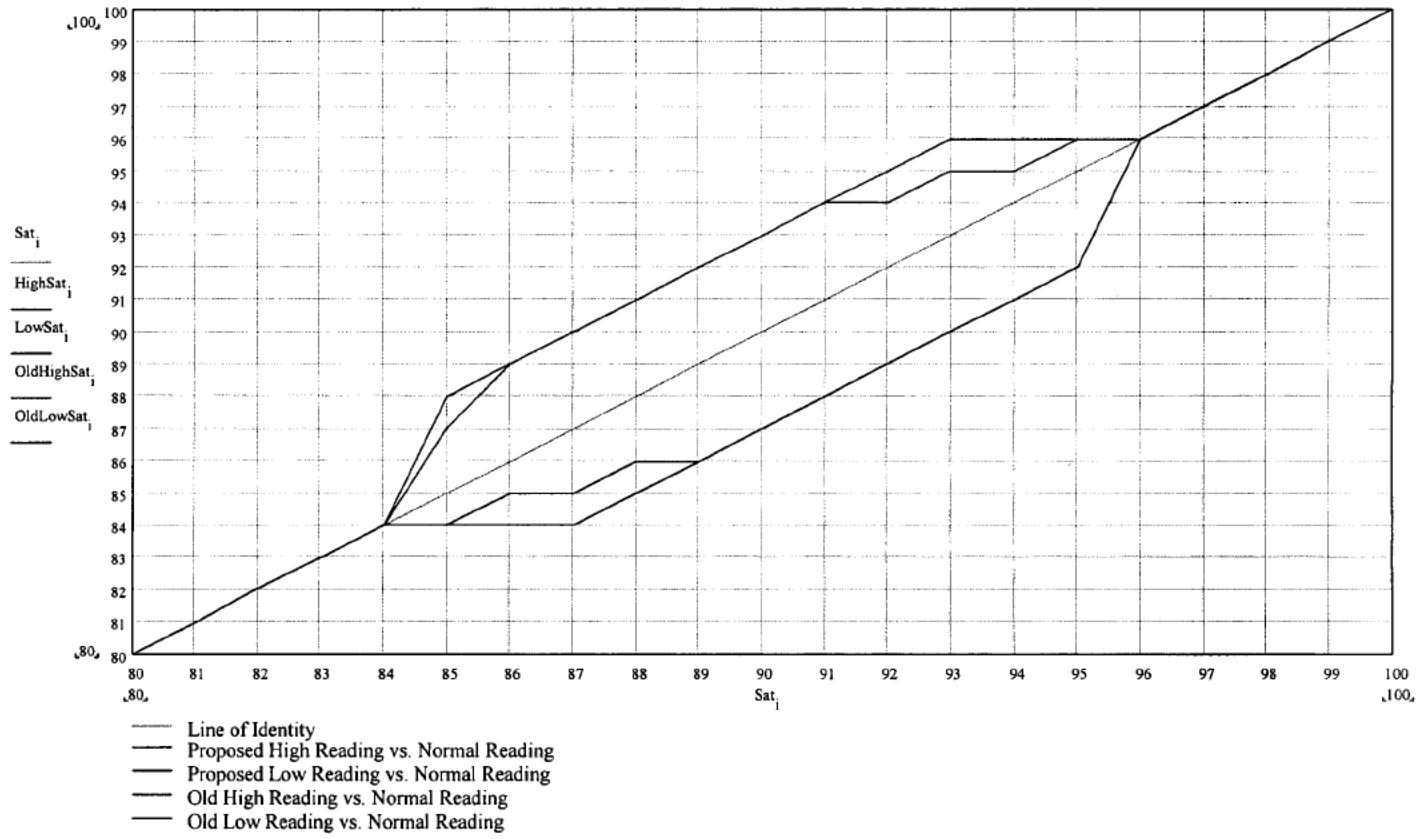
fx. (301) 230-4646

Converting Actual Readings to Low and High Readings

Actual Reading	To Low Reading	To High Reading
100	100	100
99	99	99
98	98	98
97	97	97
96	96	96
95	92	96
94	91	96
93	90	96
92	89	95
91	88	94
90	87	93
89	86	92
88	85	91
87	84	90
86	84	89
85	84	88
84	84	84
83	83	83
82	82	82
81	81	81
80	80	80
etc	etc	etc



The Low, Actual & High Reading oximeters synchronize for values greater than or equal to 96 % and less than or equal to 84 %.

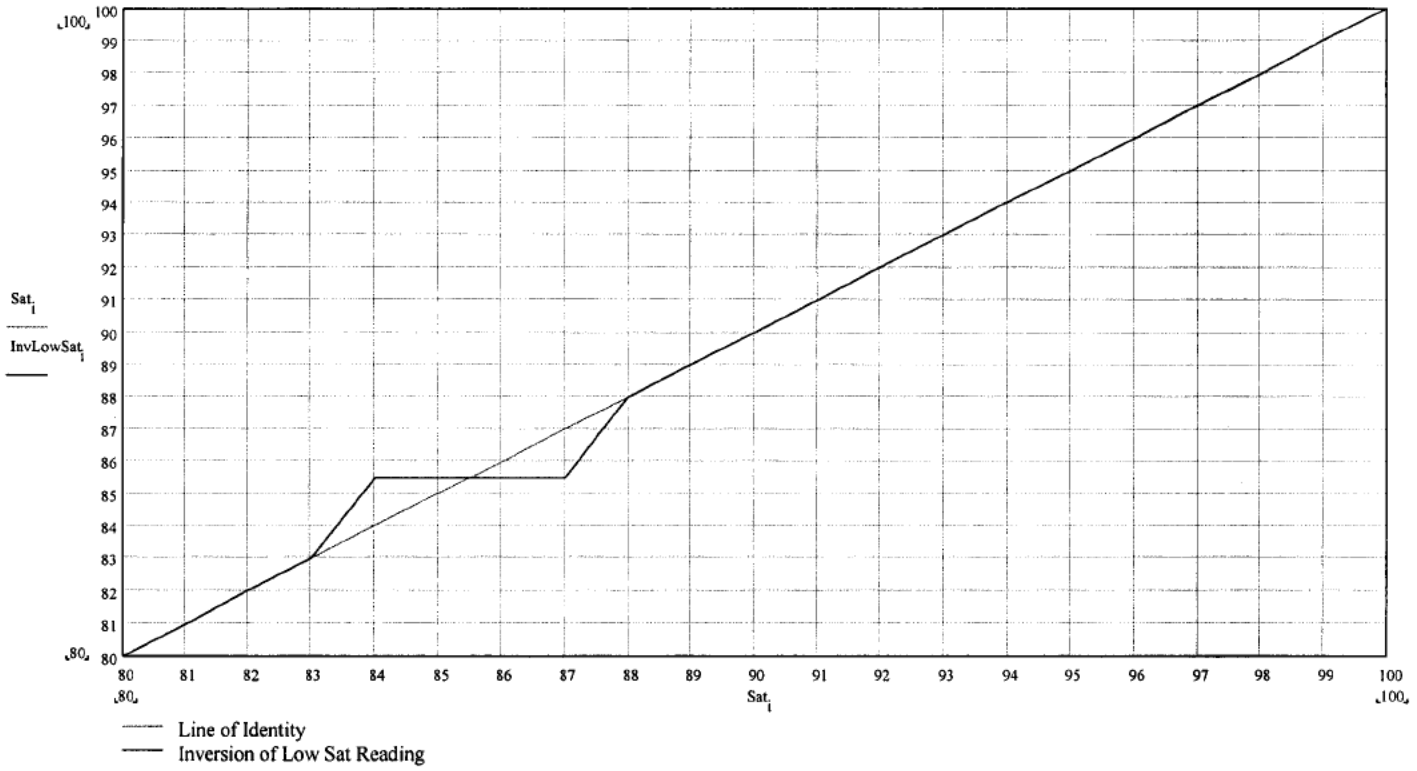
In the Actual range of 87 % to 95 %, the Low Reading Oximeter displays a value 3 points below actual.

In the Actual range of 85 % to 93 %, the High Reading Oximeter displays a value 3 points above actual.

Converting Low Readings to Normal Readings

Low Reading	To Normal Reading
100	100
99	99
98	98
97	97
96	96
95	95.75
94	95.50
93	95.25
92	95
91	94
90	93
89	92
88	91
87	90
86	89
85	88
84	85.5
83	83
82	82
81	81
80	80
etc	etc

Applying the above inversion yields the following performance:

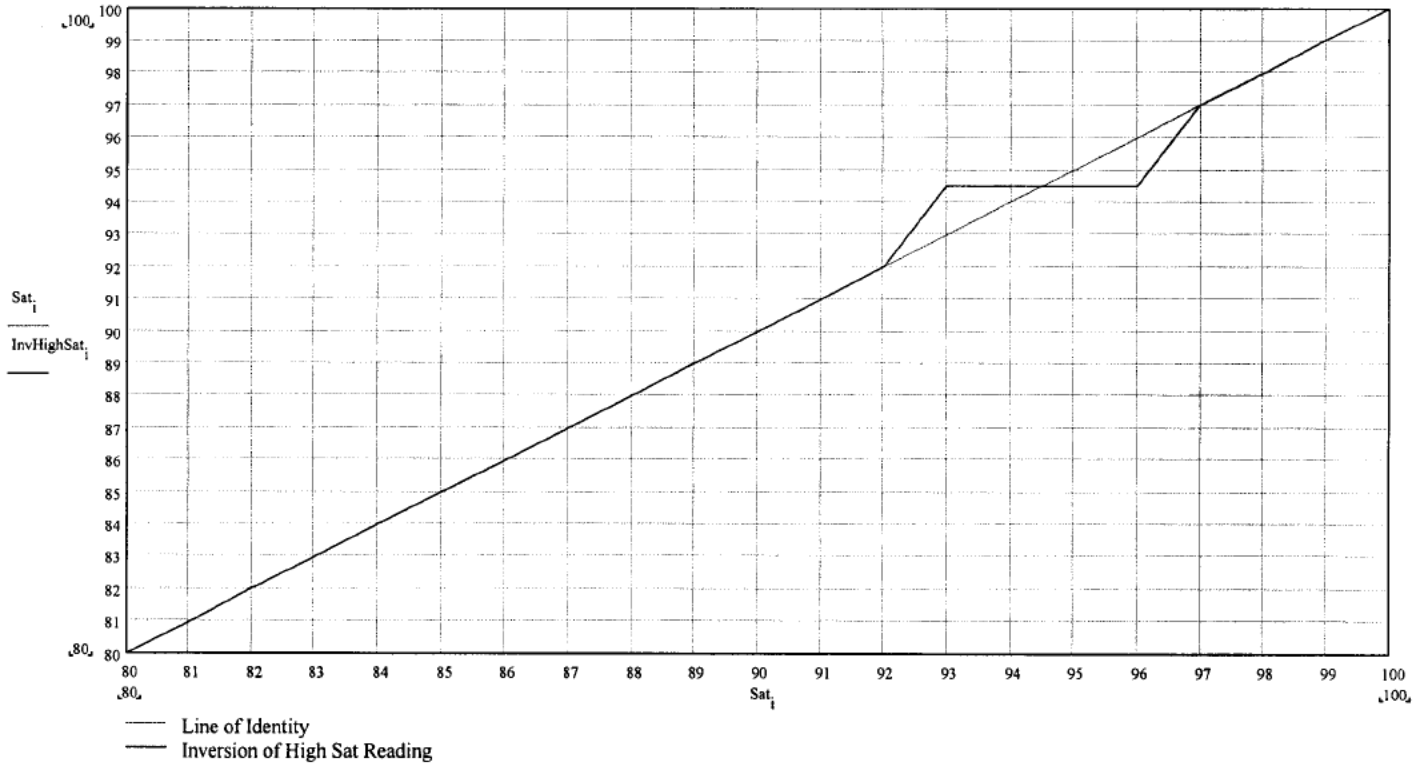


The inversion has no error above and below an actual reading of 88 % and 83 %, respectively. In between these limits, the inversion error does not exceed 1.5 %. Subjects are typically kept in the region of 91 % (88 % + 3 %) to 95 % (92 % + 3 %).

Converting High Readings to Actual Readings

High Reading	To Actual Reading
100	100
99	99
98	98
97	97
96	94.5
95	92
94	91
93	90
92	89
91	88
90	87
89	86
88	85
87	84.75
86	84.50
85	84.25
84	84
83	83
82	82
81	81
80	80
etc	etc

Applying the above inversion yields the following performance:



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From: Michael Cotten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ronald N Goldberg
Subject: RE: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)
Date: Tuesday, November 29, 2005 10:40:04 PM
Attachments: 20040226AVIOxLateBreakerDraft.doc
Response to DSMC final for Steering Nov 29 05.doc

I think if the dsmb will be satisfied, the Duke irb will be okay w/ moving forward.

I think it's a good response.

mc

C. Michael Cotten, MD
Assistant Clinical Professor of Pediatrics
Clinical Research Director, Duke Neonatology
Director Special Care Nursery, Durham Regional Hospital
Box 3179 DUMC
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(919) 681-6025
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"Higgins, Rosemary \ (NIH/NICHD\)" <higginsr@mail.nih.gov>
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cc: <aellison@med.miami.edu>, <echaisso@iupui.edu>, <bvecchio@careNE.org>, (b) (6) <debra.camputaro@yale.edu>, <diane.timmer@cchmc.org>, <fmartinez@ucsd.edu>, <Karen.Kirby@UTsouthwestern.edu>, <Ktownsen@med.wayne.edu>, <KGilley@careNE.org>, <lisa.joo@stanford.edu>, <msumner@peds.uab.edu>, "[SCRN] Tinsley, Mazie" <mazie_tinsley@oz.ped.emory.edu>, "[SCRN] Dunbar-Scott, Renee" <renee.dunbar-scott@oz.ped.emory.edu>, "Jensen, Rosemary" <Rosemary_Jensen@urmc.rochester.edu>,

<gonza025@mc.duke.edu>, "Wendy Holcomb" <wholcomb@wfubmc.edu>

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LATE BREAKER ABSTRACT SUBMISSION FORM

Abstracts and Payment must be RECEIVED by March 1, 2004

~ Abstracts must be submitted electronically using this form.
~ Abstracts, inclusive of title, authors, institutions, and graphs/tables, must fit in a 6.5 inch x 4 inch space between the two lines (appx. 2,600 characters). Use a font no smaller than 10 pt.
~ You must complete all information and include payment ($50 US) for your abstract to be considered.

Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation

J Hagadorn [1,2], A Furey [1], TH Nghiem [1], S Greene [1], E Abban [1], J Cho [1], P Shrestha [1], A Vora [1], M Landa [2], C Schmid [2], P Hibberd [2], CH Cole [1] and The AVIOx Study Group. [1]Div Newborn Med and [2]Div of Clin Care Research, Tufts-New England Med Ctr, Boston, MA.

Background: Detailed data are not available regarding the actual versus intended SpO2 in infants born <28 weeks gestation (extremely premature newborns, EPNs) in the neonatal period during routine care. **Objective:** To document actual SpO2 in EPNs in the first 4 weeks of life during routine care and compare to the level recommended by local policy/guideline. **Design/Methods:** EPNs <96 hours old were enrolled in a prospective multicenter cohort study. Oximetry data were collected every 2 seconds with masked signal-extraction oximeters for 72 hours in each of the first four weeks of life. Data were compared to SpO2 range prescribed by local institutional policy. **Results:** 14 centers from 3 countries enrolled 78 infants with mean birth weight 863 g (SD 208 g) and mean gestational age 26 wk (SD 1.4 wk). Lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for median of 70 hours (25^{th}-75^{th} percentiles 67-71 hr) in each week. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25^{th}-75^{th} percentiles 91-97; range of study center medians 91-96). Centers ranged between 16-71% compliance with intended SpO2 range. Most noncompliance was above intended range. **Conclusions:** Compliance with intended SpO2 range during routine care varied substantially among participating centers, and was generally poor regardless of intended level. These data will assist quality improvement and education efforts, and will aid planning of prospective randomized trials examining level of oxygenation. **Disclosure:** Funded by the SPR Student Research Program; Fight for Sight/Prevent Blindness America; The Tufts-NEMC Research Fund; GCRC/Natl Center for Research Resources MO1-RR00054, and NEI K23 EY/HD00420. Oximeters provided by Masimo Corp.

Briefly describe the reason why the December deadline could not be met:
Study still in progress at December deadline, with only about 60% of enrollment achieved.

Person to whom all communication should be addressed: James Hagadorn, MD

Complete Mailing Address: 750 Washington Street, Tufts-NEMC #44
Boston, MA 02111 USA

Telephone: 617.636.4193 Facsimile: 617.636.1456

Email: jhagadorn@tufts-nemc.org

First Author is a member of: __APS __SPR __APA __ASPHO __ASPN __LWPES

Conflict of Interest/Disclosure Statement/Approval of All Authors

Work submitted for presentation must include an acknowledgement of funding sources of commercial nature and/or consulting or holding of significant equity in a company that could be affected by the results of the study. The intent of this policy is not to prevent a speaker with a potential conflict of interest from making a presentation, it is merely intended that any potential conflict should be identified openly so that the listeners may form their own judgments about the presentation with the full disclosure of the facts. *Even if indicated elsewhere in the abstract, this must appear as the last sentence of the abstract and read "funded by..." and/or "equity in..." if pertinent.*

By emailing this electronic file, you verify that: You have the approval of all authors to submit this work for presentation; this work will not have been previously published in manuscript format; any animal studies conform with the "Guiding Principles in the Care and Use of Animals" of the American Physiological Society and any human experimentation has been conducted according to a protocol approved by the institutional committee on ethics of human investigation or if no such committee exists, that it conforms with the principles of the Declaration of Helsinki of the World Medical Association (CLINICAL RESEARCH 14:193, 1966)

Signature of First Author, attesting to the above: _____

Final Submission Steps:

- Attach this file to an email and send to: datwood@aps-spr.org
- Fax a copy of this form to PAS Late Breakers, 281-419-0082 along with your payment form

Questions? Call, 281-419-0052

In response to the comments and concerns of the DSMC, the SUPPORT committee held a conference call Monday Nov 28th at 10:00 to 1130AM to prepare a response.

- The DSMC made the following 2 comments in their letter regarding the SUPPORT trial. This was generated after they reviewed the oximeter data, which was corrected back to actual SpO2 values from the altered values displayed at the bedside:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

We have responded to each of these concerns and our responses are detailed below

Response to Issue Number 1

We appreciate the concern expressed by the DSMC regarding a potential safety issue secondary to durations of SpO2 values > 95%. To date there are no prospective data which define the SpO2s experienced by the ELBW infant from birth as part of usual clinical care. Because no published studies have evaluated the effects of different target SpO2 ranges on important outcomes, this was one of the principle reasons for the design and conduct of the SUPPORT trial. A number of studies have evaluated different alarm limits, but have not reported the actual durations of SpO2 in the various ranges. Nghiem et al in a PAS abstract this year reported that nurses caring for ELBW infants believe that an acceptable oxygen saturation range should include higher upper limits than specified by current policy (Nghiem et al, Nursing Opinions and Practices of Oxygenation in Prematures: The NOPOP Study PAS #3415, 2005). The study by Hagadorn reported as a late breaker at the PAS this year (Hagadorn et al, Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation. PAS 2005, Attached) did report on the experience of monitoring the actual SpO2 for 72 hours in the first 4 weeks of life in 72 ELBW infants. They reported that the "lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for a median of 70 hours (25th-75th percentiles 67-71 hr) during each week. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25th-75th percentiles 91-97; range of study center medians 91-96). Centers ranged between 16-71% compliance with their individual intended SpO2 range. Most noncompliance was above intended range." In comparing the data evaluated to date by the DSMC, it is of interest that the mean SpO2 in the 2 Oximeter arms is 90% and 92%, with

medians of 92% and 94%, all of which are below that reported by Hagadorn et al (median=95). The 2 other relevant trials, STOP-ROP and BOOST, both enrolled infants at about 32 weeks PCA, and maintained 2 levels of SpO2, 89% to 94% and 91-94% versus 95% to 98% and 96% to 99%, by administration of oxygen. These studies achieved reasonable separation, but did demonstrate approximately 25% overlap of the intended ranges. It is important to note that these studies were testing two ranges both of which were higher than the lower range of the SUPPORT trial (85% to 89%) and were treating infants who, for the most part, had recovered from their acute disease. In the BOOST trial 70% were < 28 weeks of age at birth (all of SUPPORT is < 28 weeks), 32 weeks postmenstrual age (PMA), and required oxygen at enrollment (Askie et al New England Journal of Medicine. 2003; 349(10):959-967). The STOP-ROP trial enrolled infants with pre-threshold ROP at a PMA of 35.4 + 2.5 weeks of age (Phelps et al Pediatrics. 2000; 105(2):295-310). These trials then gave the higher SpO2 range infants additional oxygen to increase their SpO2 to the desired range. STOP-ROP reported that the infants in the high range had an SpO2 > 95% for > 97% of the monitored time. These studies found an overall increase in pulmonary morbidity in the higher SpO2 range infants.

The oximetry algorithm that was designed for this trial is such that re-conversion of the altered oximeter values does not result in a discrete SpO2 number for every displayed value. SpO2 values, of 93%, 94% 95% and 96% will all be reconverted to a single value in one arm , while 84%, 85%, 86% and 87% will be reconverted to a single value in the other arm. This is a result of having the displayed values return to non-skewed SpO2 values at < 84% and > 96%, a safety design felt to be important by all involved in this trial. Thus the percentages shown that was shown for some of the ranges that include these values were not an accurate representation of the true values. However all values > 96% and < 84% are actual and do not require any conversion.

Percent of time of spent at SpO2 < 84% and > 96%
(RTI, Nov 29, 2005, 14:00 Hrs)

Range	High target (91-95)	Low target (85-89)
< 84%	8.51	16.62
> 96%	22.69	13.60

In the current SUPPORT study, initial analyses utilizing only unaltered SpO2 values as shown above , ie those below 84% and above 96% have shown that one arm had an SpO2 > 96% for 13.6% versus 22.69% of the time for the comparison arm, and the durations of an SpO2 < 84% was also different at 16.62% versus 8.51%. The previously reported value of 36% duration of an SpO2 > 95% represented an artifact of the conversion algorithm as described above. The values for SpO2s > 96% using unaltered data suggests that the SUPPORT trial to date has, if anything, reduced the duration of hyperoxia.

In addition, using these values which represent actual SpO2 values, we can state that the infants in this trial are spending approximately 70% of the time

with a true SpO2 value between 84% and 96%. We believe that this is information is very encouraging, and suggests that if we are able to further improve adherence to the target ranges that we will achieve an adequate separation between the groups.

As part of the SUPPORT trial, we collect information about inhaled oxygen concentration 3 times a day for the first 14 days and daily thereafter. We believe that a more frequent documentation of inhaled oxygen will allow us to determine the actual duration of oxygen exposure. At the present an infant is considered to be receiving supplemental oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized as receiving supplemental oxygen for significant periods when they are actually in room air. This would result in durations of SpO2 greater than 95% that were felt to be modifiable and reported as such when in fact there is no effective treatment for such elevated SpO2s. In addition, we do not know if such SpO2s on room air are associated with any morbidity. From the SUPPORT study data analyses to date we know that infants in room air have SpO2s > 95% for 46% to 69% of the time.

In view of this design, we would suggest that all future analyses evaluate the ranges of <84% and >96% as those ranges that are considered to be low and high.

We believe that the SUPPORT trial will actually define the periods of time that ELBW infants spend with different ranges of SpO2, and that it is essential to collect these data. In addition, as our findings indicate a lower true percent of the time at SpO2 values >95% than has been reported, we are in fact, reducing the time with high SpO2 values compared to usual care. The SUPPORT trial carefully evaluates risks, and we will be evaluating group differences for all important short and long term outcomes.

The SUPPORT trial methodology actively encourages all caretakers to keep SpO2 < 96% by having alarm limits set at 85% to 95%. These limits were utilized because it was felt that these represented current practice. The oximetry algorithms were designed to keep infants in the narrower target range of 88% to 92% with the realization that setting alarm limits at these values would severely increase the frequency of the alarms sounding. Nevertheless, our results to date suggest that we have decreased the expected percent of time > 95%, and in one group this value of 14% may be as low as is achievable in an actual clinical environment.

We believe that the SUPPORT study will define the durations of high and low SpO2 and will be able to determine if there is a threshold duration of either value that is associated with altered outcomes, and for this reason alone, the SUPPORT trial will be very valuable. All of the procedures outlined below in response to your second concern will also allow us to further increase the percentage of time that the infants are in the maximally altered SpO2 ranges which we believe will further increase separation of these groups.

Response to Issue Number 2

There is concern that we have not achieved adequate separation by the current oximeters and study personnel. Reviewing the newest analyses available as described above, there are differences in the durations of low and high SpO2s between the 2 oximeter groups. We do acknowledge that it would desirable to increase the percentage of time in the narrower target range and towards this end would propose the following changes to SUPPORT:

1. We will require documentation that the alarm limits are set and functional as per protocol every 4-6 hours. We have found that in some units the high alarms are being defeated, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned to the respiratory therapists, and this procedure is already being done in many NRN units.

2. We will collect FiO2 data more frequently, and at a minimum every 4 hours while the infant is requiring oxygen or any form of assisted ventilation. In the current protocol we collect such information 3 times a day for the first 14 days only and then daily thereafter. We believe that more frequent documentation will allow us to determine the actual time that an infant is in room air. At the present the infant is considered in oxygen if he/she requires oxygen for greater than intermittent use. This results in infants being categorized in oxygen for significant periods when they are in room air. While in room air, we cannot manipulate the SpO2, and thus knowledge of the true time in oxygen will produce a more accurate representation of oximetry results that are subject to care interventions.

3. We will initiate further training and in-service at all the sites to stress the importance of keeping the SpO2 alarm functional and at the limits of 85% and 95%. In the past these were guidelines, and we will now change the study manual and protocol to indicate these limits are now set by protocol and that violations will be documented. We will encourage all caretakers to aim for an SpO2 value of 90% and make every effort to make smaller adjustments in FiO2 and ensure that the infant is maintained between the 87% to 93%, the range with the maximal separation of the study oximeters. We will further facilitate the use of the 2 hour and 12 hour histograms showing the infants' actual ranges to provide feedback to the caretakers regarding the percentage of time in the target ranges.

4. We will develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation. We would hope that such changes – ie increasing the FiO2 in steps of 5% as opposed to much larger increases will decrease the resultant overshoots creating the high SpO2 values. This will be included in the revised manual of operations.

5. We will place bedside cards to indicate the target range.

At the present time servo controlled oxygen monitoring is not clinically available, and assigning a separate caretaker to adjust oxygen alone is impractical. In

addition neither of these interventions would represent available care at this time, and the results would not be generalizeable.

We trust that our plans to move forward with the SUPPORT trial are acceptable to the DSMC. We are anxious to initiate the above changes, seek IRB approvals and re-activate this trial.

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE:
Date: Tuesday, November 29, 2005 9:33:45 PM

My duty and pleasure
Thanks Rose

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 29, 2005 4:57 PM
To: nfiner@ucsd.edu
Subject: Re:

Fine
Thanks again for all the thought and effort for this trial.

Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Tue Nov 29 19:55:32 2005
Subject: RE:

Hi Rose
No. I sent that email with the SUPPORT Committee only.
I think that what you sent was perfect.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 29, 2005 4:49 PM
To: nfiner@ucsd.edu
Subject: Re:

Neil
Did you want me to share the body of this email with the steering committee?
I just sent the two attachments out.

Thanks for all the hard work, and effort that has gone into this!
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: 'Avroy A. Fanaroff, M.D.' <aaf2@po.cwru.edu>; 'Betty Hastings' <bkh@rti.org>; 'Ed Donovan' <Edward.Donovan@chmcc.org>; Higgins, Rosemary

(NIH/NICHD) <higginsr@mail.nih.gov>; 'Ken Poole' <poo@rti.org>;
'Michele'
<mcw3@po.cwru.edu>; 'Neil Finer' <nfiner@ucsd.edu>; 'Shahnaz Duara'
<sduara@miami.edu>; 'Wade Rich' <wrich@ucsd.edu>; 'Wally Carlo'
<wcarlo@peds.uab.edu>
CC: 'MD' 'Maynard Rasmussen' <Maynard.Rasmussen@sharp.com>; Neil Finer
<nfiner@pedsmail.ucsd.edu>; 'Gantz, Marie' <mgantz@rti.org>; 'Das,
Abhik'
<adas@rti.org>
Sent: Tue Nov 29 18:49:38 2005
Subject:

Hello Rose and Everyone

Well I just completed my last call of the day with Marie. She was very helpful, and my thanks to her and Scott for the additional data runs.

These runs proved critical and as we suspected removing the altered values
resulted in a completely different picture for SpO2s > 95%. Ultimately I
have chosen to represent the unaltered values, ie those > 96% and < 84% as
these are always real. If we now calculate the times we find that we are >
96% for about 23% in 1 arm and 14% in the other. On the low side, in parallel, we have SpO2s < 84% for 8% and 16%. Note that we do have Separation!!

Interpreted differently we are between 84% and 96% almost 70% of the time.
I think that this is very good. There is no safety issue as we do not have
excessive times of high SpO2s by anyone's definition. I have rewritten the
document, and included the recent summary data. In addition I will attach
the Hagadorn Abstract as this is not easily found.

Rose, would you please circulate these to the Steering Committee?

Many thanks to you all!!

I am confident that we can move ahead and I feel much better about this trial, and especially the oximeter arm.

Be well and stay tuned

Neil

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)
Date: Tuesday, November 29, 2005 7:49:10 PM

Thanks Rose
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 29, 2005 4:44 PM
To: Petrie, Carolyn; wrich@ucsd.edu; Hastings, Betty J.; Zaterka-Baxter, Kristin; Alice.J.Reardon@uth.tmc.edu; nirupama_laroia@urmc.rochester.edu; Walid.Salhab@UTsouthwestern.edu; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; D'Angio, Carl; Brenda Poindexter; Brenda.H.Morris@uth.tmc.edu; Krisa Van Meurs; Gantz, Marie; Poole, W. Kenneth; [SCRN] Stoll, Barbara; Charles.Rosenfeld@UTsouthwestern.edu; dale_phelps@urmc.rochester.edu; Das, Abhik; dstevenson@stanford.edu; edward.donovan@chmcc.org; goldb008@mc.duke.edu; jlemons@iupui.edu; Jobea0@chmcc.org; jon.e.tyson@uth.tmc.edu; alaptook@WIHRI.org; mcw3@cwru.edu; moshea@wfubmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; sduara@miami.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; WOh@WIHRI.org; D'Angio, Carl; ambal@sprynet.com
Cc: aellison@med.miami.edu; echaisso@iupui.edu; bvecchio@careNE.org; (b) (6); debra.camputaro@yale.edu; diane.timmer@cchmc.org; fmartinez@ucsd.edu; Karen.Kirby@UTsouthwestern.edu; Ktownsen@med.wayne.edu; KGilley@careNE.org; lisa.joo@stanford.edu; msumner@peds.uab.edu; [SCRN] Tinsley, Mazie; [SCRN] Dunbar-Scott, Renee; Jensen, Rosemary; gonza025@mc.duke.edu; Wendy Holcomb
Subject: RE: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)

Hi
For the morning call, I have attached the response from Neil Finer and the SUPPORT Subcommittee. Please read this over before the call if time permits. Also attached is a late breaker abstract from PAS looking at saturation data in premature infants. If you are unable to make the call, please insure that your alternate PI or another representative for your site is on the call. This is CRUCIAL for input and a DSMC response.

Thanks for all your help.

Rose

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Tue 11/29/2005 4:55 PM
To: Petrie, Carolyn; wrich@ucsd.edu; Hastings, Betty J.; Zaterka-Baxter, Kristin; Alice.J.Reardon@uth.tmc.edu; nirupama_laroia@urmc.rochester.edu; Walid.Salhab@UTsouthwestern.edu; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; D'Angio, Carl; Brenda Poindexter; Brenda.H.Morris@uth.tmc.edu; Krisa Van Meurs; Gantz, Marie; Poole, W. Kenneth; [SCRN] Stoll, Barbara; Charles.Rosenfeld@UTSouthwestern.edu; dale_phelps@urmc.rochester.edu; Das, Abhik; dstevenson@stanford.edu;

edward.donovan@chmcc.org; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD); jlemons@iupui.edu; Jobea0@chmcc.org; jon.e.tyson@uth.tmc.edu; alaptook@WIHRI.org; mcw3@cwru.edu; moshea@wfubmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; sduara@miami.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; WOh@wihri.org; D'Angio, Carl; ambal@sprynet.com
Cc: aellison@med.miami.edu; echaisso@iupui.edu; bvecchio@careNE.org; (b) (6); debra.camputaro@yale.edu; diane.timmer@cchmc.org; fmartinez@ucsd.edu; Karen.Kirby@UTSouthwestern.edu; Ktownsen@med.wayne.edu; KGilley@CareNE.org; lisa.joo@stanford.edu; msumner@peds.uab.edu; [SCRN] Tinsley, Mazie; [SCRN] Dunbar-Scott, Renee; Jensen, Rosemary; gonza025@mc.duke.edu; Wendy Holcomb
Subject: RE: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)

Reminder for tomorrow's call:

The NRN conference call to discuss potential strategies to resume the SUPPORT Trial is scheduled for

Wednesday, November 30th

9:30-10:30am ET (6:30-7:30am PT)

To join the call,

Dial Toll Free, 866-675(b) (6)

Passcode: (b) (6)

PIs: Please ensure that every center is represented for this call.

Carolyn Petrie Huitema

Neonatal Research Network Coordinator

RTI International

6110 Executive Blvd

Suite 902

Rockville, MD 20852

ph. (301) 230-4648

fx. (301) 230-4646

From:	Neil Finer
To:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Cc:	"MD" "Maynard Rasmussen"; Neil Finer; "Gantz, Marie"; "Das, Abhik"
Date:	Tuesday, November 29, 2005 6:49:57 PM
Attachments:	20040226AVIOxLateBreakerDraft.doc Response to DSMC final for Steering Nov 29 05.doc

---

Hello Rose and Everyone

Well I just completed my last call of the day with Marie. She was very helpful, and my thanks to her and Scott for the additional data runs.

These runs proved critical and as we suspected removing the altered values resulted in a completely different picture for SpO2s > 95%. Ultimately I have chosen to represent the unaltered values, ie those > 96% and < 84% as these are always real. If we now calculate the times we find that we are > 96% for about 23% in 1 arm and 14% in the other. On the low side, in parallel, we have SpO2s < 84% for 8% and 16%. Note that we do have Separation!!

Interpreted differently we are between 84% and 96% almost 70% of the time. I think that this is very good. There is no safety issue as we do not have excessive times of high SpO2s by anyone's definition. I have rewritten the document, and included the recent summary data. In addition I will attach the Hagadorn Abstract as this is not easily found.

Rose, would you please circulate these to the Steering Committee?

Many thanks to you all!!

I am confident that we can move ahead and I feel much better about this trial, and especially the oximeter arm.

Be well and stay tuned

Neil

LATE BREAKER ABSTRACT SUBMISSION FORM

Abstracts and Payment must be RECEIVED by March 1, 2004

~ Abstracts must be submitted electronically using this form.
~ Abstracts, inclusive of title, authors, institutions, and graphs/tables, must fit in a 6.5 inch x 4 inch space between the two lines (appx. 2,600 characters). Use a font no smaller than 10 pt.
~ You must complete all information and include payment ($50 US) for your abstract to be considered.

Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation

J Hagadorn [1,2], A Furey [1], TH Nghiem [1], S Greene [1], E Abban [1], J Cho [1], P Shrestha [1], A Vora [1], M Landa [2], C Schmid [2], P Hibberd [2], CH Cole [1] and The AVIOx Study Group. [1]Div Newborn Med and [2]Div of Clin Care Research, Tufts-New England Med Ctr, Boston, MA.

Background: Detailed data are not available regarding the actual versus intended SpO2 in infants born <28 weeks gestation (extremely premature newborns, EPNs) in the neonatal period during routine care. **Objective:** To document actual SpO2 in EPNs in the first 4 weeks of life during routine care and compare to the level recommended by local policy/guideline. **Design/Methods:** EPNs <96 hours old were enrolled in a prospective multicenter cohort study. Oximetry data were collected every 2 seconds with masked signal-extraction oximeters for 72 hours in each of the first four weeks of life. Data were compared to SpO2 range prescribed by local institutional policy. **Results:** 14 centers from 3 countries enrolled 78 infants with mean birth weight 863 g (SD 208 g) and mean gestational age 26 wk (SD 1.4 wk). Lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for median of 70 hours (25^{th}-75^{th} percentiles 67-71 hr) in each week. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25^{th}-75^{th} percentiles 91-97; range of study center medians 91-96). Centers ranged between 16-71% compliance with intended SpO2 range. Most noncompliance was above intended range. **Conclusions:** Compliance with intended SpO2 range during routine care varied substantially among participating centers, and was generally poor regardless of intended level. These data will assist quality improvement and education efforts, and will aid planning of prospective randomized trials examining level of oxygenation. **Disclosure:** Funded by the SPR Student Research Program; Fight for Sight/Prevent Blindness America; The Tufts-NEMC Research Fund; GCRC/Natl Center for Research Resources MO1-RR00054, and NEI K23 EY/HD00420. Oximeters provided by Masimo Corp.

Briefly describe the reason why the December deadline could not be met:
Study still in progress at December deadline, with only about 60% of enrollment achieved.

Person to whom all communication should be addressed: James Hagadorn, MD

Complete Mailing Address: 750 Washington Street, Tufts-NEMC #44
Boston, MA 02111 USA

Telephone: 617.636.4193 Facsimile: 617.636.1456

Email: jhagadorn@tufts-nemc.org

First Author is a member of: __APS __SPR __APA __ASPHO __ASPN __LWPES

Conflict of Interest/Disclosure Statement/Approval of All Authors

Work submitted for presentation must include an acknowledgement of funding sources of commercial nature and/or consulting or holding of significant equity in a company that could be affected by the results of the study. The intent of this policy is not to prevent a speaker with a potential conflict of interest from making a presentation, it is merely intended that any potential conflict should be identified openly so that the listeners may form their own judgments about the presentation with the full disclosure of the facts. *Even if indicated elsewhere in the abstract, this must appear as the last sentence of the abstract and read "funded by..." and/or "equity in..." if pertinent.*

By emailing this electronic file, you verify that: You have the approval of all authors to submit this work for presentation; this work will not have been previously published in manuscript format; any animal studies conform with the "Guiding Principles in the Care and Use of Animals" of the American Physiological Society and any human experimentation has been conducted according to a protocol approved by the institutional committee on ethics of human investigation or if no such committee exists, that it conforms with the principles of the Declaration of Helsinki of the World Medical Association (CLINICAL RESEARCH 14:193, 1966)

Signature of First Author, attesting to the above: _____

Final Submission Steps:

- Attach this file to an email and send to: datwood@aps-spr.org
- Fax a copy of this form to PAS Late Breakers, 281-419-0082 along with your payment form

Questions? Call, 281-419-0052

In response to the comments and concerns of the DSMC, the SUPPORT committee held a conference call Monday Nov 28th at 10:00 to 1130AM to prepare a response.

- The DSMC made the following 2 comments in their letter regarding the SUPPORT trial. This was generated after they reviewed the oximeter data, which was corrected back to actual SpO2 values from the altered values displayed at the bedside:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

We have responded to each of these concerns and our responses are detailed below

Response to Issue Number 1

We appreciate the concern expressed by the DSMC regarding a potential safety issue secondary to durations of SpO2 values > 95%. To date there are no prospective data which define the SpO2s experienced by the ELBW infant from birth as part of usual clinical care. Because no published studies have evaluated the effects of different target SpO2 ranges on important outcomes, this was one of the principle reasons for the design and conduct of the SUPPORT trial. A number of studies have evaluated different alarm limits, but have not reported the actual durations of SpO2 in the various ranges. Nghiem et al in a PAS abstract this year reported that nurses caring for ELBW infants believe that an acceptable oxygen saturation range should include higher upper limits than specified by current policy (Nghiem et al, Nursing Opinions and Practices of Oxygenation in Prematures: The NOPOP Study PAS #3415, 2005). The study by Hagadorn reported as a late breaker at the PAS this year (Hagadorn et al, Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation. PAS 2005, Attached) did report on the experience of monitoring the actual SpO2 for 72 hours in the first 4 weeks of life in 72 ELBW infants. They reported that the "lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for a median of 70 hours (25th-75th percentiles 67-71 hr) during each week. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25th-75th percentiles 91-97; range of study center medians 91-96). Centers ranged between 16-71% compliance with their individual intended SpO2 range. Most noncompliance was above intended range." In comparing the data evaluated to date by the DSMC, it is of interest that the mean SpO2 in the 2 Oximeter arms is 90% and 92%, with

medians of 92% and 94%, all of which are below that reported by Hagadorn et al (median=95). The 2 other relevant trials, STOP-ROP and BOOST, both enrolled infants at about 32 weeks PCA, and maintained 2 levels of SpO2, 89% to 94% and 91-94% versus 95% to 98% and 96% to 99%, by administration of oxygen. These studies achieved reasonable separation, but did demonstrate approximately 25% overlap of the intended ranges. It is important to note that these studies were testing two ranges both of which were higher than the lower range of the SUPPORT trial (85% to 89%) and were treating infants who, for the most part, had recovered from their acute disease. In the BOOST trial 70% were < 28 weeks of age at birth (all of SUPPORT is < 28 weeks), 32 weeks postmenstrual age (PMA), and required oxygen at enrollment (Askie et al New England Journal of Medicine. 2003; 349(10):959-967). The STOP-ROP trial enrolled infants with pre-threshold ROP at a PMA of 35.4 + 2.5 weeks of age (Phelps et al Pediatrics. 2000; 105(2):295-310). These trials then gave the higher SpO2 range infants additional oxygen to increase their SpO2 to the desired range. STOP-ROP reported that the infants in the high range had an SpO2 > 95% for > 97% of the monitored time. These studies found an overall increase in pulmonary morbidity in the higher SpO2 range infants.

The oximetry algorithm that was designed for this trial is such that re-conversion of the altered oximeter values does not result in a discrete SpO2 number for every displayed value. SpO2 values, of 93%, 94% 95% and 96% will all be reconverted to a single value in one arm , while 84%, 85%, 86% and 87% will be reconverted to a single value in the other arm. This is a result of having the displayed values return to non-skewed SpO2 values at < 84% and > 96%, a safety design felt to be important by all involved in this trial. Thus the percentages shown that was shown for some of the ranges that include these values were not an accurate representation of the true values. However all values > 96% and < 84% are actual and do not require any conversion.

Percent of time of spent at SpO2 < 84% and > 96%
(RTI, Nov 29, 2005, 14:00 Hrs)

Range	High target (91-95)	Low target (85-89)
< 84%	8.51	16.62
> 96%	22.69	13.60

In the current SUPPORT study, initial analyses utilizing only unaltered SpO2 values as shown above , ie those below 84% and above 96% have shown that one arm had an SpO2 > 96% for 13.6% versus 22.69% of the time for the comparison arm, and the durations of an SpO2 < 84% was also different at 16.62% versus 8.51%. The previously reported value of 36% duration of an SpO2 > 95% represented an artifact of the conversion algorithm as described above. The values for SpO2s > 96% using unaltered data suggests that the SUPPORT trial to date has, if anything, reduced the duration of hyperoxia.

In addition, using these values which represent actual SpO2 values, we can state that the infants in this trial are spending approximately 70% of the time

with a true SpO2 value between 84% and 96%. We believe that this is information is very encouraging, and suggests that if we are able to further improve adherence to the target ranges that we will achieve an adequate separation between the groups.

As part of the SUPPORT trial, we collect information about inhaled oxygen concentration 3 times a day for the first 14 days and daily thereafter. We believe that a more frequent documentation of inhaled oxygen will allow us to determine the actual duration of oxygen exposure. At the present an infant is considered to be receiving supplemental oxygen if he/she requires oxygen for greater than 2 hours. This results in infants being categorized as receiving supplemental oxygen for significant periods when they are actually in room air. This would result in durations of SpO2 greater than 95% that were felt to be modifiable and reported as such when in fact there is no effective treatment for such elevated SpO2s. In addition, we do not know if such SpO2s on room air are associated with any morbidity. From the SUPPORT study data analyses to date we know that infants in room air have SpO2s > 95% for 46% to 69% of the time.

In view of this design, we would suggest that all future analyses evaluate the ranges of <84% and >96% as those ranges that are considered to be low and high.

We believe that the SUPPORT trial will actually define the periods of time that ELBW infants spend with different ranges of SpO2, and that it is essential to collect these data. In addition, as our findings indicate a lower true percent of the time at SpO2 values >95% than has been reported, we are in fact, reducing the time with high SpO2 values compared to usual care. The SUPPORT trial carefully evaluates risks, and we will be evaluating group differences for all important short and long term outcomes.

The SUPPORT trial methodology actively encourages all caretakers to keep SpO2 < 96% by having alarm limits set at 85% to 95%. These limits were utilized because it was felt that these represented current practice. The oximetry algorithms were designed to keep infants in the narrower target range of 88% to 92% with the realization that setting alarm limits at these values would severely increase the frequency of the alarms sounding. Nevertheless, our results to date suggest that we have decreased the expected percent of time > 95%, and in one group this value of 14% may be as low as is achievable in an actual clinical environment.

We believe that the SUPPORT study will define the durations of high and low SpO2 and will be able to determine if there is a threshold duration of either value that is associated with altered outcomes, and for this reason alone, the SUPPORT trial will be very valuable. All of the procedures outlined below in response to your second concern will also allow us to further increase the percentage of time that the infants are in the maximally altered SpO2 ranges which we believe will further increase separation of these groups.

Response to Issue Number 2

There is concern that we have not achieved adequate separation by the current oximeters and study personnel. Reviewing the newest analyses available as described above, there are differences in the durations of low and high SpO2s between the 2 oximeter groups. We do acknowledge that it would desirable to increase the percentage of time in the narrower target range and towards this end would propose the following changes to SUPPORT:

1. We will require documentation that the alarm limits are set and functional as per protocol every 4-6 hours. We have found that in some units the high alarms are being defeated, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned to the respiratory therapists, and this procedure is already being done in many NRN units.

2. We will collect FiO2 data more frequently, and at a minimum every 4 hours while the infant is requiring oxygen or any form of assisted ventilation. In the current protocol we collect such information 3 times a day for the first 14 days only and then daily thereafter. We believe that more frequent documentation will allow us to determine the actual time that an infant is in room air. At the present the infant is considered in oxygen if he/she requires oxygen for greater than intermittent use. This results in infants being categorized in oxygen for significant periods when they are in room air. While in room air, we cannot manipulate the SpO2, and thus knowledge of the true time in oxygen will produce a more accurate representation of oximetry results that are subject to care interventions.

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5. We will place bedside cards to indicate the target range.

At the present time servo controlled oxygen monitoring is not clinically available, and assigning a separate caretaker to adjust oxygen alone is impractical. In

addition neither of these interventions would represent available care at this time, and the results would not be generalizeable.

We trust that our plans to move forward with the SUPPORT trial are acceptable to the DSMC. We are anxious to initiate the above changes, seek IRB approvals and re-activate this trial.

From: Petrie, Carolyn
To: Petrie, Carolyn; wrich@ucsd.edu; Hastings, Betty J.; Zaterka-Baxter, Kristin; Alice.J.Reardon@uth.tmc.edu; nirupama_laroia@urmc.rochester.edu; Walid.Salhab@UTsouthwestern.edu; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; D"Angio, Carl; Brenda Poindexter; Brenda.H.Morris@uth.tmc.edu; Krisa Van Meurs; Gantz, Marie; Poole, W. Kenneth; [SCRN] Stoll, Barbara; Charles.Rosenfeld@UTSouthwestern.edu; dale_phelps@urmc.rochester.edu; Das, Abhik; dstevenson@stanford.edu; edward.donovan@chmcc.org; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; jlemons@iupui.edu; Jobea0@chmcc.org; jon.e.tyson@uth.tmc.edu; alaptook@WIHRI.org; mcw3@cwru.edu; moshea@wfubmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; sduara@miami.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; WOh@wihri.org; D"Angio, Carl; ambal@sprynet.com
Cc: aellison@med.miami.edu; echaisso@iupui.edu; bvecchio@careNE.org; (b) (6) debra.camputaro@yale.edu; diane.timmer@cchmc.org; fmartinez@ucsd.edu; Karen.Kirby@UTSouthwestern.edu; Ktownsen@med.wayne.edu; KGilley@CareNE.org; lisa.joo@stanford.edu; msumner@peds.uab.edu; [SCRN] Tinsley, Mazie; [SCRN] Dunbar-Scott, Renee; Jensen, Rosemary; gonza025@mc.duke.edu; Wendy Holcomb
Subject: RE: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)
Date: Tuesday, November 29, 2005 4:55:19 PM

Reminder for tomorrow's call:

The NRN conference call to discuss potential strategies to resume the SUPPORT Trial is scheduled for

Wednesday, November 30th
9:30-10:30am ET (6:30-7:30am PT)

To join the call,

Dial Toll Free, 866-675-(b) (6)
Passcode: (b) (6)

PIs: Please ensure that every center is represented for this call.

Carolyn Petrie Huitema
Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
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Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From:	Duara, Shahnaz
To:	nfiner@ucsd.edu
Cc:	adas@rti.org; wcarlo@peds.uab.edu; edward.donovan@cchmc.org; poo@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Michele Walsh
Subject:	Response to DSMC Revision Nov 29 05 SD comments.doc
Date:	Tuesday, November 29, 2005 4:13:57 PM
Attachments:	Response to DSMC Revision Nov 29 05 SD comments.doc

Hi Neil,

The arguments have been well made. I agree with Ed's comments and have added some points.
Hope they are helpful.

Shahnaz
<<Response to DSMC Revision Nov 29 05 SD comments.doc>>

In response to the comments and concerns of the DSMC, the SUPPORT committee held a conference call Monday Nov 28th at 10:00 to 1130AM to prepare a response.

- The DSMC made the following 2 comments in their letter regarding the SUPPORT trial. This was generated after they reviewed the oximeter data, which was corrected back to actual SpO2 values from the altered values displayed at the bedside:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

We have responded to each of these concerns and our responses are detailed below

Response to Issue Number 1

We appreciate the concern expressed by the DSMC regarding a potential safety issue secondary to durations of SpO2 values > 95%. To date there are no prospective data which define the ~~normal~~ SpO2s experienced by the ELBW infant from birth as part of usual clinical care. Because n~~There have been no~~ published studies have evaluated the effects of~~comparisons of~~ different target SpO2 ranges on~~which have evaluated~~ important outcomes, ~~and~~ this was one of the principle reasons for the design and conduct of the SUPPORT trial. A number of studies~~units~~ have evaluated different~~altered their~~ alarm limits, but have not reported ~~on~~ the actual durations of SpO2 in the various ranges. The study by Hagadorn reported as a late breaker at the PAS last year (-Attached) did report on the experience of monitoring the actual SpO2 for 72 hours in the first 4 weeks of life in 72 ELBW infants. They reported that the "-lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for a median of 70 hours (25th-75th percentiles 67-71 hr) during~~in~~ each week. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25th-75th percentiles 91-97; range of study center medians 91-96). Centers ranged between 16-71% compliance with their individual intended SpO2 range. Most noncompliance was above intended range." ~~The median SpO2 in that study was 95%.~~ In comparing the data evaluated to date by the DSMC, it is of interest that the median SpO2 in the 2 Oximeter arms is 90% and 92% well below that reported by Hagadorn et al (median=95%). Data from a single center in the NRN ~~was also reviewed~~ for 9 ELBW infants receiving usual clinical care ~~and that study~~ revealed that these ~~s~~ infants had an SpO2 > 95% for 56% of the time with a range of 38% to 86% (-Walsh, Case Western). The 2

other relevant trials, STOP-ROP and BOOST, both enrolled infants at about 32 weeks PCA, and maintained 2 levels of SpO2, 89% to 94% or 91-94% versus 95% to 98% and 96% to 99%, by administration of oxygen, using oximetry. These studies ~~were able to~~ achieved reasonable separation, but did demonstrate approximately 25% overlap of the intended ranges. It is important to note that these studies were testing ~~the~~ ranges both of which were higher than the lower range of the SUPPORT trial (~~-~~85% to 89%) and were treating infants who, ~~were~~ for the most part, were older, had recovered from ~~over~~ their acute disease, and required oxygen at enrollment . 70% of infants ~~whom~~ in BOOST were < 28 weeks of age at birth (~~-~~all of SUPPORT is < 28 weeks) and ~~who were~~ 32 weeks postmenstrual age (PMA) ~~and required oxygen at enrollment~~. The STOP-ROP trial enrolled infants with pre-threshold ROP at a PMA of 35.4 ± 2.5 weeks of age. These trials then gave the targeted higher SpO2 range infants additional oxygen to increase their SpO2 to the desired range. STOP-ROP reported that the infants in the high range had an SpO2 > 95% for > 97% of the monitored time. These studies found an overall increase in pulmonary morbidity in the higher SpO2 range infants.

In the current SUPPORT study, ~~the~~ initial analyses have shown that one group had an SpO2 > 95% for 14% versus 36% of the time for the comparison arm. Neither of these values is as high as that reported by Hagadorn or found by Walsh, and both are significantly below that found in the BOOST and STOP-ROP trials. Indeed, of interest is the fact that there this degree of separation ~~was such a wide separation~~ in ~~the~~ acutely ill ELBW infants during their initial treatment with oxygen and other ventilatory ~~type of~~ support [I don't understand this last sentence].

As part of the SUPPORT trial, ~~In the current protocol~~ we collect ~~such~~ information about inhaled oxygen concentration ~~administration~~ 3 times a day for the first 14 days only and then daily thereafter. We believe that a closer documentation of inhaled oxygen will allow us to determine the actual duration~~time that an infant is in~~ of room air exposure. At the present, the infant is considered to be in supplemental oxygen if he/she requires oxygen for greater than intermittent use and has supplemental oxygen use documented at least once a day. Therefore ~~This results in~~ infants can be ~~being~~ categorized as in supplemental oxygen for significant periods when they are in room air. This ~~would~~ can result in durations of SpO2 greater than 95% that are interpreted to ~~were felt to~~ be modifiable by clinical care ~~and reported as such~~ when in fact there is no effective treatment for such normally high ~~elevated~~ SpO2s. ~~In addition, we do not know if such SpO2 on room air are associated with any morbidity.~~ From the SUPPORT study data analyses to date we know that infants in room air have SpO2s > 95% for 46% to 69% of the time.

The oximetry algorithm that was designed for this trial is such that re-conversion of ~~the~~ altered oximeter values does not result in ~~an~~ actual SpO2 values for every displayed value. This paradox is explained thus: ~~Thus~~ there are a number of SpO2 values, ie 93%, 94% 95% and 96% which ~~will~~ all result in the same ~~a single~~ value (96%) being represented when converted from displayed to actual values for one range, and for the other range values of 84%, 85%, 86%

and 87% (84%) will also be represented by a single value. This is a result of having the displayed values return to actual SpO2 values < 84% and > 96%, a safety design felt to be important by all involved in this trial. This results in ~~the fact the percentages shown for some of the~~ ranges that include these values to be~~being a~~ less than accurate representation of the true values, since values close to the point where altered values revert to real values have adjusted points superimposed upon true values. A~~However a~~ll values > 96% and < 84% are actual, since the algorithm does not affect these points. In view of this design, we would suggest that all future analyses evaluate the ranges of <84% and ->96%, as those ranges ~~that~~ are irrefutable true measures of ~~considered to be~~ low and high oxygenation.

We do not believe that the time spent > 95%-, 36% for one of the randomized groups,~~,~~ is significantly different from current experience in the care of the ELBW infant. In the SUPPORT Pilot that assessed the design of the oximeter algorithm, we found in 20 infants, all of whom met SUPPORT criteria, that the distribution of SpO2 was greater than 93% for 49% of the time. This was a study of only 12 to 24 hours per child.

We believe that the SUPPORT trial will actually define the periods of time that ELBW infants spend with different ranges of SpO2, and that it is essential to collect these~~is~~ data. In addition, as our findings indicate a lower percent of the time at SpO2 values >95% than has been reported, that we are in fact, reducing the time with high SpO2 values compared to usual care. In addition,- the actual separation that we are seeing suggests that we are achieving in some measure a difference between the groups.

The SUPPORT trial ~~will~~ carefully evaluates ~~the~~ risks, and we will be evaluat~~analyz~~ing group differences for all important short and long term outcomes..

The SUPPORT trial methodology actively encourages all caretakers to keep ~~the infants~~ SpO2 < 96% by having alarm limits set at 85% to 95%. These limit~~numbers~~ were utilized because it was felt that these represented current practice. The oximetry algorithms were designed to keep ~~the~~ infants in the narrower target range of 88% to 92% with the realization that setting alarm limits at these values would severely increase the frequency of the alarms sounding. Nevertheless, our results to date suggest that we have decreased the expected percent of time > 95%, and in one group this value of 14% may be as low as is achievable in an actual clinical environment.

There is also a 10% difference in the time that the infants are below 85%, and this may be an important difference.

We believe that the SUPPORT study will define the durations of high and low SpO2 and will be able to determine if there is a threshold duration of either value that is associated with altered outcomes, and for this reason alone, the SUPPORT trial will be very valuable. All of the procedures outlined below in response to your second concern will also allow us to further increase the percentage of time that the infants are in the maximally altered SpO2 ranges which we believe will further increase separation of these groups.

Response to Issue Number 2

There is concern that we have not achieved adequate separation by the current oximeters and study personnel. As pointed out above, we have achieved differences in the time spent at both high and low SpO2 ranges for the first 153 infants. We are not aware of whether these 2 groups differ by their oxygen exposure, as this has not yet been analyzed. It is however possible that the current differences could result in differences in outcomes, both short and longer term.

It is biologically plausible that higher SpO2 values have a greater impact on oxygen-associated morbidities. That our "usual care" group (SpO2 target 91-95%) spends more than twice as much time in with SpO2 greater than 95% compared to the study group (SpO2 target 85-89%) suggests that we have good "separation" for the purpose of identifying preventable oxygen-associated morbidities.

We do acknowledge that a greater range of separation would be desirable and towards this end would propose the following changes to SUPPORT:

1. We will require documentation that the alarm limits are set and functional as per protocol every 4-6 hours. We have found that in some units the high alarms are being defeated, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned to the respiratory therapists, and this procedure is already being done on some NRN units.

2. We will collect FiO2 data every hour while the infant is requiring oxygen or any form of assisted ventilation. In the current protocol we collect such information 3 times a day for the first 14 days only and then daily thereafter. We believe that a closer documentation will allow us to determine the actual time that an infant is in room -air. At the present the infant is considered in oxygen if he/she requires oxygen for greater than intermittent use. This results in infants being categorized in oxygen for significant periods when they are in room air. While in room air, we cannot manipulate the SpO2, and thus knowledge of this value will assist us in knowing the true time in oxygen. [we may only need to this for a smaller sample of study subjects and therefore reduce coordinator effort]

3.. We will initiate further in-service at all the sites to stress the importance of keeping the SpO2 alarm functional and at the limits of 85% and 95%. In the past these were guidelines, and we will now change the study manual and protocol to indicate these limits are now set by protocol and that violations will be documented.

4. We will develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation. We would hope that such changes

– ie increasing the FiO2 in steps of 5% as opposed to much larger increases will decrease the resultant overshoots creating the high SpO2 values. This will be included in the revised manual of operations.

5. We will place bedside cards to indicate the target range.

At the present time servo controlled oxygen monitoring is not clinically available, and assigning a separate caretaker to adjust oxygen alone is impractical. In addition neither of these interventions would represent available care at this time, and the results would not be generalizeable.

We trust that our plans to move forward with the SUPPORT trial are acceptable to the DSMC. We are anxious to initiate the above changes, seek IRB approvals and re-activate this trial.

From: Julie Di Fiore
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: rxm6@po.cwru.edu
Subject: Desaturation data for NON SUPPORT infants
Date: Tuesday, November 29, 2005 1:58:38 PM
Attachments: 2006 Pediatric Academic Societies" and Eastern SPR Annual Meetings.mht
percent ranges.xls

Dear Rose,

It was a pleasure speaking to you. Considering how long oxygen saturation has been monitored over the years it is amazing how much there is to learn even regarding basic practice.

I have included 2 attachments. The first attachment is a copy of the Desaturation abstract in progress. The format is a bit clumsy but it seems to be the best option I could find in which to save the document. The second attachment is an Excel spreadsheet including our 9 NON SUPPORT infants and the time in each target range. The spread sheet includes 2 tables, one in which all days were included and the second in which days in RA were deleted. The tables included data from DOL 1 to 32 wks of age so there are 4-8wks of data for each infant depending on their GA.

If you have any questions or other requests feel free to contact me via email or phone (see below).

Best Regards,

Julie

Juliann Di Fiore
Research Engineer
Rainbow Babies & Children's Hospital
Division of Neonatology
11100 Euclid Ave
Cleveland, OH 44106
phone: (216) 844-1478
Fax: (216) 844-3380

Preview Abstract

Draft Preview of Abstract #750947
THIS COPY IS A DRAFT ONLY. YOUR FINAL PRINTOUT WILL BE AVAILABLE AT TIME OF SUBMISSION

First Author: Juliann M Di Fiore

Presenting Author: Juliann M Di Fiore

Responsible Author: Juliann M Di Fiore

Subspecialty: Neonatology - General

Theme: Neonatal - Patient-Oriented Research

2006 Pediatric Academic Societies' Meeting

Consider for Eastern SPR: No, Do not consider this abstract for the Eastern SPR.

Contact Person: Juliann M Di Fiore, BSEE

Department/Institution/Address: Pediatrics, Rainbow Babies and Children's Hospital, 11100 Euclid Ave, Cleveland, Ohio, 44106, United States

Phone: 216 844-1478 **Fax:** 216 844-3380 **E-mail:** jmd3@po.cwru.edu

Presenter E-mail: jmd3@po.cwru.edu

Responsible Author E-mail: jmd3@po.cwru.edu

Awards Applied for:
Consider for PAS Travel Grant Award: No

APA Special Interest Groups, Committees or Regions:

Is Presenting Author a Trainee? No, Not a Trainee
Research type: Clinical
Presentation conflict on: No conflict

Title: Progessive Increase in Incidence of Episodic Desaturation in Very Low Birth Weight Infants during the First Month of Life

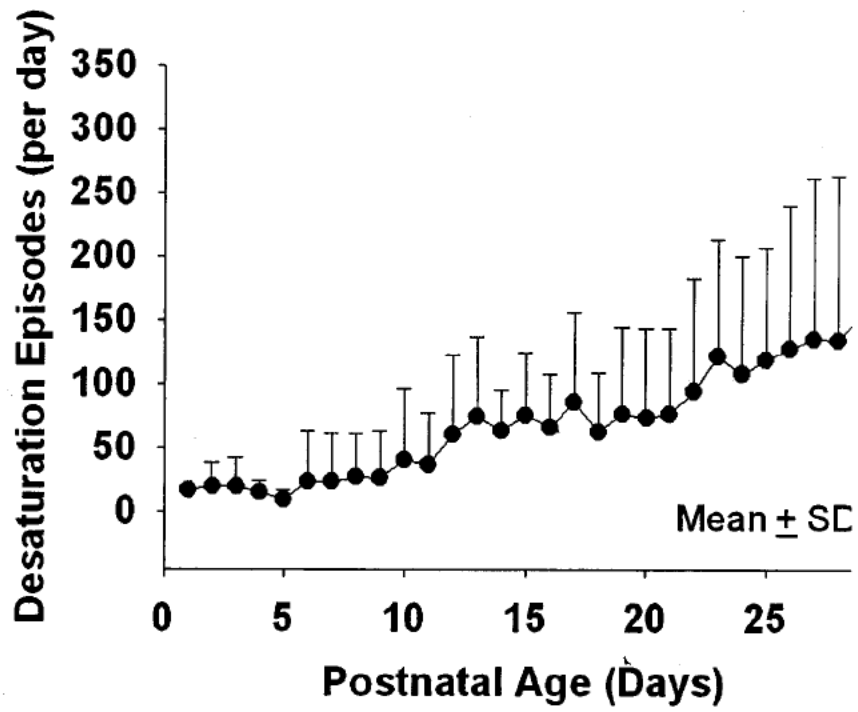
Juliann M Di Fiore, BSEE[1], Arlene Zadell, BSN[1], Michele Walsh, MD[1], Wade Rich, RRT-NPS[2], Neil Finer, MD[2] and Richard J Martin, MD[1]. [1]Pediatrics, Rainbow Babies an States and [2]Pediatrics, University of California, San Diego, California, United States.

Background: Episodes of oxygen desaturation, typically a consequence of apnea or hypoventilation, are almost universal in very low birth weight (VLBW) infants. Hc incidence of such events and whether this changes in early postnatal life.

Objective: To characterize the incidence of episodic desaturation in VLBW infants over the first month of life. We hypothesized that the frequency of these episodes \ respiratory control.

Design/Methods: 9 infants, gestational age 26.1±1.3wks, birthweight 781±159gm, were enrolled in the study. While receiving normal clinical care with no study int sample rate-1 sample per 2 sec, averaging time-2 seconds) during the first 30 days of life. The number of desaturation events (defined as an SaO_2 of <80% for >10s recorded.

Results: The prevalence of episodic desaturation increased with postnatal age ($p<0001$, figure 1) from 16.8±3 to 194±137 episodes at day 1 and day 30, respectivel within a range of 91-96%. 4 infants were intubated for more than 50% of the time period (range 60-100%). The remaining 5 infants were intubated for 1-8 days. Th days (range 1-30days). 8 infants received caffeine during the study period (median 27 days, range 12-30).



Conclusions: In contrast to our hypothesis, the incidence of episodic desaturation increased over the first month of life in this preterm infant population. We specula underlying mechanism and this may overide maturation of respiratory control.

Questions about the **Online Abstract Submission process?** Contact Marathon Multimedia at Technical Support or 1-866-759-5440.

Questions about the **2006 Pediatric Academic Societies' Annual Meeting?** Contact the PAS Program Office at the PAS Program Office or 281-419-0052.

Questions about the **2006 Eastern SPR Annual Meeting?** Contact the Eastern SPR at Eastern SPR.

ALL DAYS OF MONITORING

(b) (6)	<85	85-89	90-95	>95	total
	3.1	6.4	32.9	57.7	100.1
	4	4.5	19.3	72.3	100.1
	3.5	2.4	8.3	85.6	99.8
	19.3	12.2	29.2	39.3	100
	25.4	13.1	26.4	35.1	100
	18.52	11.9	30.7	38.9	100.02
	10.2	8.7	29.4	51.7	100
	8.7	7.9	29.2	54.2	100
	4.9	4.2	24.2	66.7	100
mean	10.84667	7.922222	25.51111	55.72222	
sd	8.241578	3.87162	7.592504	16.91292	
Median	8.7	7.9	26.4	54.2	

ONLY DAYS ON O2

(b) (6)	<85	85-89	90-95	>95	total
	5	9	37	49	100
	7	9	36	47	99
	4	3	8	85	100
	19.3	12.2	29.2	39.3	100
	25.4	13.1	26.4	35.1	100
	18.52	11.9	30.7	38.9	100.02
	10.2	8.7	29.4	51.7	100
	9	8	29	54	100
	5	6	29	60	100
mean	11.49111	8.988889	28.3	51.11111	
sd	7.68334	3.192744	8.362416	15.01037	
Median	9	8.988889	29	49	

From: Wally Carlo, M.D.
To: Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Namasivayam Ambalavanan
Subject: RE: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)
Date: Tuesday, November 29, 2005 11:02:17 AM

Carolyn: I will ask Ambal. Thanks, wally

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Tuesday, November 29, 2005 8:30 AM
To: higginsr@mail.nih.gov; Wally Carlo, M.D.
Subject: FW: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)

Wally-

Yes, Marsha did tell me that you were not available. We had to find a time later this week to meet with the PIs and/or a site designee. Is someone able to join from Alabama?

Carolyn

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2005 3:33 PM
To: Petrie, Carolyn
Subject: Re: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)

Carolyn. I thought Marsha was going to tell you that I have a conflict on Wed and Tuesday. I would very much like to participate but I am in a study section.
Wally
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Petrie, Carolyn <petrie@rti.org>
To: wrich@ucsd.edu <wrich@ucsd.edu>; Hastings, Betty J. <bkh@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Alice.J.Reardon@uth.tmc.edu <Alice.J.Reardon@uth.tmc.edu>; nirupama_laroia@urmc.rochester.edu <nirupama_laroia@urmc.rochester.edu>; Walid.Salhab@UTsouthwestern.edu <Walid.Salhab@UTsouthwestern.edu>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; D'Angio, Carl <Carl_Dangio@URMC.Rochester.edu>; Brenda Poindexter <bpoindex@iupui.edu>; Brenda.H.Morris@uth.tmc.edu <Brenda.H.Morris@uth.tmc.edu>; Krisa Van Meurs <vanmeurs@stanford.edu>; Gantz, Marie <mgantz@rti.org>; Petrie, Carolyn <petrie@rti.org>; poo@rti.org <poo@rti.org>; barbara_stoll@oz.ped.emory.edu <barbara_stoll@oz.ped.emory.edu>; Charles.Rosenfeld@UTSouthwestern.edu <Charles.Rosenfeld@UTSouthwestern.edu>; dale_phelps@urmc.rochester.edu <dale_phelps@urmc.rochester.edu>; Das, Abhik <adas@rti.org>; dstevenson@stanford.edu <dstevenson@stanford.edu>; edward.donovan@chmcc.org <edward.donovan@chmcc.org>; goldb008@mc.duke.edu <goldb008@mc.duke.edu>; higginsr@mail.nih.gov <higginsr@mail.nih.gov>; jlemons@iupui.edu <jlemons@iupui.edu>; Jobea0@chmcc.org <Jobea0@chmcc.org>; jon.e.tyson@uth.tmc.edu <jon.e.tyson@uth.tmc.edu>; alaptook@WIHRI.org <alaptook@WIHRI.org>; mcw3@cwru.edu <mcw3@cwru.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; richard.ehrenkranz@yale.edu <richard.ehrenkranz@yale.edu>; sduara@miami.edu <SDuara@miami.edu>; sshankar@med.wayne.edu <sshankar@med.wayne.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; WOh@wihri.org <WOh@wihri.org>
CC: aellison@med.miami.edu <aellison@med.miami.edu>; echaisso@iupui.edu <echaisso@iupui.edu>;

bvecchio@careNE.org <bvecchio@careNE.org>; (b) (6) (b) (6) debra.camputaro@yale.edu <debra.camputaro@yale.edu>; diane.timmer@cchmc.org <diane.timmer@cchmc.org>; fmartinez@ucsd.edu <fmartinez@ucsd.edu>; Karen.Kirby@UTSouthwestern.edu <Karen.Kirby@UTSouthwestern.edu>; Ktownsen@med.wayne.edu <Ktownsen@med.wayne.edu>; KGilley@CareNE.org <KGilley@CareNE.org>; lisa.joo@stanford.edu <lisa.joo@stanford.edu>; Marsha Sumner <MSumner@peds.uab.edu>; mazie_tinsley@oz.ped.emory.edu <mazie_tinsley@oz.ped.emory.edu>; renee.dunbar-scott@oz.ped.emory.edu <renee.dunbar-scott@oz.ped.emory.edu>; Jensen, Rosemary <Rosemary_Jensen@URMC.Rochester.edu>; gonza025@mc.duke.edu <gonza025@mc.duke.edu>; Wendy Holcomb <wholcomb@wfubmc.edu>
Sent: Wed Nov 23 13:59:01 2005
Subject: SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)

The NRN conference call to discuss potential strategies to resume the SUPPORT Trial is scheduled for

Wednesday, November 30th

9:30-10:30am ET (6:30-7:30am PT)

To join the call,

Dial Toll Free, 866-675(b) (6)

Passcode: (b) (6)

PIs: Please ensure that every center is represented for this call.

Carolyn Petrie Huitema

Neonatal Research Network Coordinator

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Rockville, MD 20852

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fx. (301) 230-4646

From: Newman, Jamie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Breathing Outcomes Study
Date: Tuesday, November 29, 2005 10:26:13 AM

Ok, so I'll send out the call information for the training (Friday Dec 9 and Monday Dec 12 from 2-4) and final study documents to the group.

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 29, 2005 10:19 AM
To: Newman, Jamie
Cc: Hastings, Betty J.
Subject: RE: SUPPORT Breathing Outcomes Study

It is likely that the SUPPORT Trial will resume once approval of the protocol by the DSMC and Dr. Alexander has occurred. We should do the training as planned and the coordinators can submit the information.

Rose

From: Newman, Jamie [mailto:newman@rti.org]
Sent: Tuesday, November 29, 2005 10:17 AM
To: Higgins, Rosemary (NIH/NICHD)
Cc: Hastings, Betty J.
Subject: SUPPORT Breathing Outcomes Study

Hi Rose,
How should we proceed with the Breathing Outcomes Study? All the documents were ready to go and I was about to send out the announcement for the telephone interview training dates when the DSMC met last week. Has anyone informed Dr. Stevens about the SUPPORT Trial? Please let me know how you would like to proceed with this. I know that several of the coordinators were working on IRB submissions last week.

Thanks, Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
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From:	Neil Finer
To:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Cc:	"MD" "Maynard Rasmussen"; Neil Finer
Date:	Monday, November 28, 2005 7:11:29 PM
Attachments:	Response to DSMC Revison Nov 28 05.doc 20040226AVIOxLateBreakerDraft.doc

Hi Everyone
Sorry to be somewhat late with this but it took longer than anticipated. I have not included the section on changing the narrow target as below. On rereading we could not be certain that it added anything to the strength of our other arguments.
Please review and make any changes and get these back to me. I know that Rose wants to get this to the Steering Committee.
Thanks
Neil

. We will change the narrow target range from 88% to 92% to 86% and 94% as this represents a range where the skew is still very adequate and is just inside the alarm limits. We discussed altering the alarm limits, but these represented current practice at the time of the study, and if we can increase our time in the target range will result in adequate separation.

In response to the comments and concerns of the DSMC, the SUPPORT committee held a conference call Monday Nov 28th at 10:00 to 1130AM to prepare a response.

- The DSMC made the following 2 comments in their letter regarding the SUPPORT trial. This was generated after they reviewed the oximeter data, which was corrected back to actual SpO2 values from the altered values displayed at the bedside:

1. There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range

2. There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

We have responded to each of these concerns and our responses are detailed below

Response to Issue Number 1

We appreciate the concern expressed by the DSMC regarding a potential safety issue secondary to durations of SpO2 values > 95%. To date there are no prospective data which define the normal SpO2s experienced by the ELBW infant from birth. There have been no comparisons of different target SpO2 ranges which have evaluated important outcomes, and this was one of the principle reasons for the design and conduct of the SUPPORT trial. A number of units have altered their alarm limits, but have not reported on the actual durations of SpO2 in the various ranges. The study by Hagadorn reported as a late breaker at the PAS last year (Attached) did report on the experience of monitoring the actual SpO2 for 72 hours in the first 4 weeks of life in 72 ELBW infants. They reported that the" lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for median of 70 hours (25th-75th percentiles 67-71 hr) in each week. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25th-75th percentiles 91-97; range of study center medians 91-96). Centers ranged between 16-71% compliance with intended SpO2 range. Most noncompliance was above intended range." The median SpO2 in that study was 95%. In comparing the data evaluated to date by the DSMC it is of interest that the median SpO2 in the 2 Oximeter arms is 90% and 92% well below that reported by Hagadorn et al. Data from a single center in the NRN was also reviewed for 9 ELBW infants and that study revealed that theses infants had an SpO2 > 95% for 56% of the time with a range of 38% to 86% (Walsh, Case Western). The 2 other relevant trials, STOP-ROP and BOOST, both enrolled infants at about 32 weeks PCA, and maintained 2 levels of SpO2, 89% to 94% or 91-94% versus 95% to 98% and 96% to 99%,

by administration of oxygen, using oximetry. These studies were able to achieve reasonable separation, but did demonstrate approximately 25% overlap of the intended ranges. It is important to note that these studies were testing the ranges both of which were higher than the lower range of the SUPPORT trial (85% to 89%) and were treating infants who were for the most part over their acute disease, 70% of whom in BOOST were < 28 weeks of age at birth (all of SUPPORT is < 28 weeks) and who were 32 weeks postmenstrual age (PMA) and required oxygen at enrollment. The STOP-ROP trial enrolled infants with pre-threshold ROP at a PMA of 35.4 $\pm$ 2.5 weeks of age. These trials then gave the higher SpO2 range infants additional oxygen to increase their SpO2 to the desired range. STOP-ROP reported that the infants in the high range had an SpO2 > 95% for > 97% of the monitored time. These studies found an overall increase in pulmonary morbidity in the higher SpO2 range infants.

In the current SUPPORT study, the initial analyses have shown that one group had an SpO2 > 95% for 14% versus 36% of the time. Neither of these values is as high as that reported by Hagadorn or found by Walsh, and both are significantly below that found in the BOOST and STOP-ROP trials. Indeed, of interest is the fact that there was such a wide separation in the acutely ill ELBW infants during their treatment with oxygen and other ventilator type of support.

In the current protocol we collect such information about oxygen administration 3 times a day for the first 14 days only and then daily thereafter. We believe that a closer documentation will allow us to determine the actual time that an infant is in room air. At the present the infant is considered in oxygen if he/she requires oxygen for greater than intermittent use. This results in infants being categorized in oxygen for significant periods when they are in room air. This would result in durations of SpO2 greater than 95% that were felt to be modifiable and reported as such when in fact there is no effective treatment for such elevated SpO2s. In addition we do not know if such SpO2 on room air are associated with any morbidity. From the SUPPORT study data analyses to date we know that infants in room air have SpO2s > 95% for 46% to 69% of the time.

The algorithm that was designed for this trial is such that re-conversion of the altered oximeter values does not result in an actual SpO2 value for every displayed value. Thus there are a number of SpO2 values, ie 93%, 94% 95% and 96% which will all result in a single value being represented when converted from displayed to actual values for one range, and for the other range values of 84%, 85%, 86% and 87% will also be represented by a single value. This is a result of having the displayed values return to actual SpO2 values < 84% and > 96%, a safety design felt to be important by all involved in this trial. This results in the fact the percentages shown for some of the ranges that include these values being a less than accurate representation of the true values. However all values > 96% and < 84% are actual. In view of this design, we would suggest that all future analyses evaluate the ranges of <84% and >96% as those ranges that are considered to be low and high.

We do not believe that the time spent > 95% , 36% for one of the randomized groups,, is significantly different from current experience in the care of the ELBW infant. In the SUPPORT Pilot that assessed the design of the

oximeter algorithm, we found in 20 infants all of whom met SUPPORT criteria, that the distribution of SpO2 was greater than 93% for 49% of the time. This was a study of only12 to 24 hours per child.

We believe that the SUPPORT trial will actually define the periods of time that ELBW infants spend with different ranges of SpO2, and that it is essential to collect this data. In addition, as our findings indicate a lower percent of the time at SpO2 values >95% than has been reported, that we are in fact, reducing the time with high SpO2 values. In addition, the actual separation that we are seeing suggests that we are achieving in some measure a difference between the groups.

The SUPPORT trial will carefully evaluate the risks, and we will be analyzing group differences for all important short and long term outcomes..

The SUPPORT trial methodology actively encourages all caretakers to keep the infants SpO2 < 96% by having alarm limits set at 85% to 95%. These numbers were utilized because it was felt that these represented current practice. The algorithms were designed to keep the infants in the narrower target range of 88% to 92% with the realization that setting alarm limits at these values would severely increase the frequency of the alarms sounding. Nevertheless, our results to date suggest that we have decreased the expected percent of time > 95%, and in one group this value of 14% may be as low as is achievable in an actual clinical environment.

There is also a 10% difference in the time that the infants are below 85%, and this may be an important difference.

We believe that the SUPPORT study will define the durations of high and low SpO2 and will be able to determine if there is a threshold duration of either value that is associated with altered outcomes, and for this reason alone, the SUPPORT trial will be very valuable. All of the procedures outlined below in response to your second concern will also allow us to further increase the percentage of time that the infants are in the maximally altered SpO2 ranges which we believe will further increase separation of these groups.

Response to Issue Number 2

There is concern that we have not achieved adequate separation by the current oximeters and study personnel. As pointed out above we have achieved differences in the time spent at both high and low SpO2 ranges for the first 153 infants. We are not aware of whether these 2 groups differ by their oxygen exposure, as this has not yet been analyzed. It is however possible that the current differences could result in differences in outcomes, both short and longer term. We do acknowledge that a greater range of separation would be desirable and towards this end would propose the following changes to SUPPORT:

1. We will require documentation that the alarm limits are set and functional as per protocol every 4-6 hours. We have found that in some units the high alarms are being defeated, and thus believe that such documentation will greatly assist in decreasing the actual time that the SpO2 is > 96%. This task will be assigned

to the respiratory therapists, and this procedure is already being done on some NRN units.

2. We will collect FiO2 data every hour while the infant is requiring oxygen or any form of assisted ventilation. In the current protocol we collect such information 3 times a day for the first 14 days only and then daily thereafter. We believe that a closer documentation will allow us to determine the actual time that an infant is in room air. At the present the infant is considered in oxygen if he/she requires oxygen for greater than intermittent use. This results in infants being categorized in oxygen for significant periods when they are in room air. While in room air, we cannot manipulate the SpO2, and thus knowledge of this value will assist us in knowing the true time in oxygen.

3.. We will initiate further in-service at all the sites to stress the importance of keeping the SpO2 alarm functional and at the limits of 85% and 95%. In the past these were guidelines, and we will now change the study manual and protocol to indicate these limits are now set by protocol and that violations will be documented.

4. We will develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation. We would hope that such changes – ie increasing the FiO2 in steps of 5% as opposed to much larger increases will decrease the resultant overshoots creating the high SpO2 values. This will be included in the revised manual of operations.

5. We will place bedside cards to indicate the target range.

At the present time servo controlled oxygen monitoring is not clinically available, and assigning a separate caretaker to adjust oxygen alone is impractical. In addition neither of these interventions would represent available care at this time, and the results would not be generalizeable.

We trust that our plans to move forward with the SUPPORT trial are acceptable to the DSMC. We are anxious to initiate the above changes, seek IRB approvals and re-activate this trial.

LATE BREAKER ABSTRACT SUBMISSION FORM

Abstracts and Payment must be RECEIVED by March 1, 2004

~ Abstracts must be submitted electronically using this form.
~ Abstracts, inclusive of title, authors, institutions, and graphs/tables, must fit in a 6.5 inch x 4 inch space between the two lines (appx. 2,600 characters). Use a font no smaller than 10 pt.
~ You must complete all information and include payment ($50 US) for your abstract to be considered.

Actual vs Intended Pulse Oxygen Saturation (SpO2) in Infants <28 Weeks Gestation

J Hagadorn [1,2], A Furey [1], TH Nghiem [1], S Greene [1], E Abban [1], J Cho [1], P Shrestha [1], A Vora [1], M Landa [2], C Schmid [2], P Hibberd [2], CH Cole [1] and The AVIOx Study Group. [1]Div Newborn Med and [2]Div of Clin Care Research, Tufts-New England Med Ctr, Boston, MA.

Background: Detailed data are not available regarding the actual versus intended SpO2 in infants born <28 weeks gestation (extremely premature newborns, EPNs) in the neonatal period during routine care. **Objective:** To document actual SpO2 in EPNs in the first 4 weeks of life during routine care and compare to the level recommended by local policy/guideline. **Design/Methods:** EPNs <96 hours old were enrolled in a prospective multicenter cohort study. Oximetry data were collected every 2 seconds with masked signal-extraction oximeters for 72 hours in each of the first four weeks of life. Data were compared to SpO2 range prescribed by local institutional policy. **Results:** 14 centers from 3 countries enrolled 78 infants with mean birth weight 863 g (SD 208 g) and mean gestational age 26 wk (SD 1.4 wk). Lower limits of intended ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for median of 70 hours (25^{th}-75^{th} percentiles 67-71 hr) in each week. Overall median SpO2 for infants on supplemental O2 during the first 4 weeks was 95% (25^{th}-75^{th} percentiles 91-97; range of study center medians 91-96). Centers ranged between 16-71% compliance with intended SpO2 range. Most noncompliance was above intended range. **Conclusions:** Compliance with intended SpO2 range during routine care varied substantially among participating centers, and was generally poor regardless of intended level. These data will assist quality improvement and education efforts, and will aid planning of prospective randomized trials examining level of oxygenation. **Disclosure:** Funded by the SPR Student Research Program; Fight for Sight/Prevent Blindness America; The Tufts-NEMC Research Fund; GCRC/Natl Center for Research Resources MO1-RR00054, and NEI K23 EY/HD00420. Oximeters provided by Masimo Corp.

Briefly describe the reason why the December deadline could not be met:
Study still in progress at December deadline, with only about 60% of enrollment achieved.

Person to whom all communication should be addressed: James Hagadorn, MD

Complete Mailing Address: 750 Washington Street, Tufts-NEMC #44
Boston, MA 02111 USA

Telephone: 617.636.4193 Facsimile: 617.636.1456

Email: jhagadorn@tufts-nemc.org

First Author is a member of: __ APS __SPR __APA __ASPHO __ASPN __LWPES

Conflict of Interest/Disclosure Statement/Approval of All Authors

Work submitted for presentation must include an acknowledgement of funding sources of commercial nature and/or consulting or holding of significant equity in a company that could be affected by the results of the study. The intent of this policy is not to prevent a speaker with a potential conflict of interest from making a presentation, it is merely intended that any potential conflict should be identified openly so that the listeners may form their own judgments about the presentation with the full disclosure of the facts. *Even if indicated elsewhere in the abstract, this must appear as the last sentence of the abstract and read "funded by..." and/or "equity in..." if pertinent.*

By emailing this electronic file, you verify that: You have the approval of all authors to submit this work for presentation; this work will not have been previously published in manuscript format; any animal studies conform with the "Guiding Principles in the Care and Use of Animals" of the American Physiological Society and any human experimentation has been conducted according to a protocol approved by the institutional committee on ethics of human investigation or if no such committee exists, that it conforms with the principles of the Declaration of Helsinki of the World Medical Association (CLINICAL RESEARCH 14:193, 1966)

Signature of First Author, attesting to the above: _____

Final Submission Steps:

- Attach this file to an email and send to: datwood@aps-spr.org
- Fax a copy of this form to PAS Late Breakers, 281-419-0082 along with your payment form

Questions? Call, 281-419-0052

From: Spong, Catherine (NIH/NICHD)
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT Trial
Date: Monday, November 28, 2005 4:52:07 PM

I would (b) (5) [redacted]

Catherine Y Spong MD
Chief, Pregnancy and Perinatology Branch, NICHD, NIH
6100 Executive Blvd, Rm 4B03, MSC 7510
Bethesda MD 20892 (express mail: Rockville MD 20852)
Phone 301 435 6894 or 301 496 5575
Fax 301 496 3790
email spongc@mail.nih.gov

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD)
Sent: Monday, November 28, 2005 4:49 PM
To: Spong, Catherine (NIH/NICHD)
Subject: Fw: SUPPORT Trial

Should I tell him (b) (5) [redacted]

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Alexander, Duane (NIH/NICHD) <alexandd@exchange.nih.gov>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Mon Nov 28 16:48:14 2005
Subject: RE: SUPPORT Trial

Hi Rose –

I agree with (b) (5) [redacted].

Duane

From: Higgins, Rosemary (NIH/NICHD)
Sent: Wednesday, November 23, 2005 10:14 AM
To: Alexander, Duane (NIH/NICHD)
Cc: Spong, Catherine (NIH/NICHD); Hanson, James (NIH/NICHD)
Subject: SUPPORT Trial

Hi Duane,

I spoke to Jim Hanson regarding the SUPPORT trial enrollment suspension this AM. He suggested that (b) (5) [redacted]

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

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Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Subcommittee call Mon, Nov 28, 1-2pm ET (10-11am PT)
Date: Monday, November 28, 2005 1:05:47 PM

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we are dialing right now
Shahnaz

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 28, 2005 1:03 PM
To: Duara, Shahnaz; Michele Walsh
Subject: FW: SUPPORT Subcommittee call Mon, Nov 28, 1-2pm ET (10-11am PT)
Importance: High

Hi,
Can you join the call??
Thanks
Rose

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Wednesday, November 23, 2005 11:54 AM
To: Poole, W. Kenneth; Gantz, Marie; Hastings, Betty J.; Zaterka-Baxter, Kristin; Jobea0@chmcc.org; adas@rti.org; edward.donovan@chmcc.org; Higgins, Rosemary (NIH/NICHD); mcw3@cwru.edu; nfiner@ucsd.edu; reverett@med.miami.edu; sduara@miami.edu; wrich@ucsd.edu; wcarlo@peds.uab.edu
Cc: Petrie, Carolyn; fmartinez@ucsd.edu; aellison@med.miami.edu; diane.timmer@cchmc.org; msumner@peds.uab.edu; (b) (6)
Subject: SUPPORT Subcommittee call Mon, Nov 28, 1-2pm ET (10-11am PT)
Importance: High

The SUPPORT Subcommittee conference call is scheduled for

Monday, November 28th
1:00-2:00pm ET (10:00-11:00am PT)

To join the call,

Dial Toll Free, 866-675(b) (6)
Passcode:(b) (6)

Please note: I will schedule an NRN PI call after this subcommittee call to continue the SUPPORT trial discussion.

Carolyn Petrie Huitema
Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 902
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Charles Rosenfeld
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FW: SUPPORT conference call
Date: Monday, November 28, 2005 11:22:53 AM

I was out of town when the email came about the call. (b) (6) [redacted] therefore, Walid will be on the phone.

Charles

Charles R. Rosenfeld, M.D.
George L. MacGregor Professor of Pediatrics
and Professor of Obstetrics and Gynecology
Director, Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
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>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 11/28/05 8:41 AM >>>
Walid
Thanks very much!
Rose

-----Original Message-----
From: Walid Salhab [mailto:Walid.Salhab@UTSouthwestern.edu]
Sent: Monday, November 28, 2005 9:39 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: FW: SUPPORT conference call

Yes, Gaynelle and I will be attending the conference call. Thank you
walid

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 11/28/05 8:14 AM >>>
Hi Walid - Carolyn is away today - can you make a call on Wednesday November 30 at 9:30 AM (8:30 CST) to discuss the SUPPORT Trial? I am not sure if she had a response from you when she set the call up.
thanks
Rose

-----Original Message-----
From: Charles Rosenfeld [mailto:Charles.Rosenfeld@UTSouthwestern.edu]
Sent: Saturday, November 26, 2005 1:54 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: FW: SUPPORT conference call
Importance: High

** High Priority **

I have been out of town and did not not see the emails until today,

Saturday, Nov 26. I am in town both days, but not in the morning of Nov 30 until about 10am and not at all on Dec 1.

Sorry for the delayed response. Did Walid answer?

Charles

Charles R. Rosenfeld, M.D.
George L. MacGregor Professor of Pediatrics
and Professor of Obstetrics and Gynecology
Director, Division of Neonatal-Perinatal Medicine
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FAX: (214) 648-2481
Email: charles.rosenfeld@utsouthwestern.edu
>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 11/23/05 12:52 PM >>>
HI,

Can you let Carolyn know potential availability for the following dates for an urgent Steering Committee PI call for SUPPORT ASAP? We would like to set up the call before the end of today!!

Wed Nov 30

Thurs Dec 1

Thanks

Rose

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Wednesday, November 23, 2005 9:59 AM
To: poo@rti.org; barbara_stoll@oz.ped.emory.edu; Charles.Rosenfeld@UTSouthwestern.edu; dale_phelps@urmc.rochester.edu; Das, Abhik; dstevenson@stanford.edu; edward.donovan@chmcc.org; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD); jlemons@iupui.edu; Jobea0@chmcc.org; jon.e.tyson@uth.tmc.edu; alaptook@WIHRI.org; mcw3@cwru.edu; moshea@wfubmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; sduara@miami.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; WOh@wihri.org
Cc: Alice.J.Reardon@uth.tmc.edu; aellison@med.miami.edu; echaisso@iupui.edu; (b) (6) diane.timmer@cchmc.org; fmartinez@ucsd.edu; Karen.Kirby@UTSouthwestern.edu; debra.camputaro@yale.edu; Ktownsen@med.wayne.edu; KGilley@CareNE.org; lisa.joo@stanford.edu; msumner@peds.uab.edu; mazie_tinsley@oz.ped.emory.edu; renee.dunbar-scott@oz.ped.emory.edu;

Jensen, Rosemary; gonza025@mc.duke.edu; Wendy Holcomb; Hastings, Betty J.; Zaterka-Baxter, Kristin; Petrie, Carolyn; Gantz, Marie; wrich@ucsd.edu
Subject: SUPPORT conference call
Importance: High

Please send your availably for this urgent and important conference call regarding the SUPPORT trial.

I will schedule a SUPPORT subcommittee call first (Mon or Tues) and then a second call with the NRN PIs (Wed or Thurs).

If you are unable, please send the availability for the Alt-PI or trial PI at the site.

Mon Nov 28

Tues Nov 29

Wed Dec 1

Thurs Dec 2

Thank you!

Carolyn Petrie Huitema

Neonatal Research Network Coordinator

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From:	Neil Finer
To:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Cc:	Maynard.Rasmussen@sharp.com; "Neil Finer"
Date:	Monday, November 28, 2005 12:22:21 AM
Attachments:	Pct in each range (room air) 11-18-05.rtf DSMCMemotosites 11-22-05 adrev.doc Case Non Support data.xls Actual unmasked Pct in each O2 range 11-18-051.doc new skew Dec9 2004.doc

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Hello Everyone

In preparing for tomorrows call I thought we should have our strategy in front of us so that we alter it as needed.

Thanks for your suggestions

I have added the relevant attachments; these include the DSMC report, the data that the DSMC reviewed, the data for room air only, and Michele's data from Case.

In addition Michele sent data for 9 Non-SUPPORT infants with the SpO2 distribution:

To summarize the distribution:

> 95% sat - 56% (range 38-86)

90-95% sat - 26% (range 8-33%)

85-89% sat - 8% (range 2-13%)

< 85% sat - 11% (range 3-25%)

We also have the data from the Pilot that was done to test the algorithm separation performed at Sharp Mary Birch by Maynard.

20 recordings of ~24 hr each or ~500 hours of recording
Entry criteria identical to Support Trial
All infants on IMV or CPAP and Supplemental Oxygen
Sat alarms 84 and 96% with written orders and posted signs to keep SaO2 88-92%

Results from normal (non-skewed) Masimo oximeters:

<84%:	10% of time
84-87%:	10% of time
88-92%:	29% of time
93-96%:	40% of time
>96%:	9% of time

This is not directly comparable but shows considerable time with high SpO2. These ranges are not identical but consistent with Michele's data and the findings from the initial 153 SUPPORT infants

To review - The DSMC made the following 2 comments:

- There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range
- There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

Other relevant data – in BOOST the infants in the higher SpO2 range had SpO2s> 95% for 90% of the time. These were infants who were unable to maintain SpO2 > 94% in room air

In reviewing the DSMC comments I believe that our strategy moving forward should be as follows:

1. We should strenuously argue that the percent of time over 95% in NOT a safety issue as there is no antecedent data that such SpO2s for such a duration, ie 35% > 95% are toxic. We would argue that this duration is actually lower than may be expected.
2. We would additionally hope that an analysis will show excessive time at 96% which actually may represent values from 93% to 96%. This will also be true for the value of 84% which may be over-represented. This is a phenomenon of back converting the algorithm when trying to determine true SpO2 values from the altered oximeters. I have attached the actual skew as an attachment.
3. I would suggest that we change the low alarm to 80% and the high to 94%. This should push us toward the narrow targets
4. We need to develop increased in-service at all sites to encourage keeping infants in the narrower ranges of 88% to 92% - Signs at bedside, rewards by histogram results, and monthly recognition of the units with the best target data. Please suggest any mechanisms that you think would be effective
5. We need to rewrite the manual and protocol to clarify that we are aiming to produce different oxygen exposures using different SpO2 limits
6. I would suggest that we collect more FiO2 data. I would assume that all units keep hourly FiO2 data for all infants on ventilators and CPAP. I would propose that we collect hourly data for at least the first 14 days for all such infants and try to continue to collect such data for all infants who require oxygen via any mechanism. For prongs we would collect flow and and FiO2, and daily weight. We do have technology to continuously record FiO2. I will briefly discuss this – we could do this for the next 10-20 infants or more and compare with the SpO2 data. Please think about this.
7. I would fight vigorously to continue the trial as is, and re-evaluate the oximetry data after a further 100-200 infants
8. If we are forced to consider dropping the oximetry arm, then I would propose that we have all the Masimo oximeters converted to normal and continue to use them to collect the data about the actual SpO2 exposures of this population which will still be unique and incredibly useful in looking at durations of hyperoxia and hypoxia in the ELBW and their outcomes.
9. Other possibilities – redesign of the algorithm going below 85%, using a 3-5% SpO2 offset without correction for 1 arm, and standard oximeters for the other. I believe that Masimo was reluctant to design such an offset on the belief that clinicians would want to know the true SpO2 of an infant if below 85%.

Thanks for staying tuned. Talk to you in the morning.
Be well
Neil

HIGH TREATMENT GROUP: PERCENT OF TIME SPENT IN EACH O2 RANGE DAYS ON ROOM AIR*

LOW TREATMENT GROUP

Center Number	Total number of hours	<85	Low target 85-89	90	High target 91-95	>95	Mean O2 level
		2.8	4.1	1.6	37.7	53.7	95.6
		5.1	5.0	1.9	45.3	42.6	94.4
		6.5	7.2	2.5	42.6	41.2	94.3
		5.1	7.4	2.7	43.2	41.5	94.5
		3.0	4.9	1.8	46.7	43.6	95.0
		6.4	6.4	2.2	44.7	40.3	94.4
Total	**14193.2**	**4.5**	**5.5**	**2.0**	**42.0**	**46.1**	**94.8**

HIGH TREATMENT GROUP

Center Number	Total number of hours	<85	Low target 85-89	90	High target 91-95	>95	Mean O2 level
		1.3	4.5	1.8	27.0	65.4	95.9
		1.9	4.5	1.5	23.0	68.9	95.7
		2.9	4.3	1.4	23.8	67.6	95.4
		7.0	7.0	1.9	20.8	63.3	94.4
		1.0	3.7	1.5	28.4	65.4	95.6
		1.5	2.7	1.0	15.7	79.1	96.7
		2.0	3.8	1.3	19.3	73.5	96.1
Total	**12414.1**	**2.9**	**4.5**	**1.5**	**22.5**	**68.8**	**95.6**

*Days on room air are defined as FiO2=0.21 or Mode of Support=7 (No Support) on SUPP05 or Oxygen=N or Highest Level of Support=7 (No Support) on SUPP11.

Centers with <500 hours are not show but are included in the total.

DEPARTMENT OF HEALTH & HUMAN SERVICES National Institutes of Health

National Institute of Child Health and Human Development

November 22, 2005

MEMORANDUM

T0: Institutional Review Boards of the Neonatal Research Network (NRN) Sites

FROM: Gordon Avery, MD
Chair of the Data Safety and Monitoring Committee (DSMC) of the NRN (as prepared by the Data Coordinating Center)

SUBJECT: Summary of the November 22, 2005 Data Safety and Monitoring Committee Conference Call

The DSMC for the Neonatal Research Network had a teleconference meeting at 11:00AM on November 22, 2005 to review data on oxygen saturations ranges from the SUPPORT Trial. Attached is a summary of the DSMC deliberations for this study.

cc: Rose Higgins
Alan Jobe
NICHD Neonatal Research Network PIs
NICHD Neonatal Research Network Coordinators
DSMC Members

Attachment

NEONATAL RESEARCH NETWORK

DATA SAFETY AND MONITORING COMMITTEE

DRAFT MINUTES

November 22, 1005

The Data Safety and Monitoring Committee for the Neonatal Research Network met via teleconference at 11:00AM on November 22, 2005 to discuss and review data from the oxygen saturation arm of the SUPPORT Trial. The DSMC members in attendance were Drs. Avery (chair), Boyle, Gleason, Redmond, Willinger, Hunt and Allen. Drs. Das and Gantz and Ms. Hastings and Ms. Zarterka-Baxter from the Data Center were also present.

Tables representing the percent of time spent in each O2 range (days on supplemental O2 only) for each of the low and high treatment groups were previously e-mailed to the Committee prior to the call. These tables were based on study data as of November 7, 2005 (153 study subjects).

After reviewing and discussing these data, the DSMC expressed significant concern about the following two issues:

- There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range
- There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

NOTE: Dr Dwyane Alexander, Director of NICHD, reviewed the above recommendation and discussed the specifics with Dr. Rose Higgins, Program Scientist for the Neonatal Research Network, and after thorough consideration of all of the issues, agreed with the recommendation and requested that enrollment be temporarily suspended into the trial until one can assure that the oxygen saturations are in the planned target range. Sites were notified on November 22, 2005 that enrollment should be temporarily suspended until further notice.

(b) (6)	<85	85-89	90-95	>95	total
	3.1	6.4	32.9	57.7	100.1
	4	4.5	19.3	72.3	100.1
	3.5	2.4	8.3	85.6	99.8
	19.3	12.2	29.2	39.3	100
	25.4	13.1	26.4	35.1	100
	18.52	11.9	30.7	38.9	100.02
	10.2	8.7	29.4	51.7	100
	8.7	7.9	29.2	54.2	100
	4.9	4.2	24.2	66.7	100
mean	10.84667	7.922222	25.51111	55.72222	
sd	8.241578	3.87162	7.592504	16.91292	

PERCENT OF TIME SPENT IN EACH O2 RANGE
(DAYS ON SUPPLEMENTAL OXYGEN ONLY)

LOW TREATMENT GROUP

Center	<85	Low target 85-89	90	High target 91-95	>95	Mean O2 level
	13.5	11.6	3.5	51.8	19.4	91.5
	8.6	16.0	4.6	45.5	25.3	92.4
	12.5	5.4	1.7	70.0	10.4	91.6
	20.1	20.6	5.7	44.2	9.5	89.6
	18.2	16.2	4.7	47.5	13.3	90.0
	19.9	25.1	4.6	37.5	12.8	89.0
	21.0	18.8	5.3	42.2	12.6	89.0
	14.8	18.3	5.8	50.5	10.4	90.7
	15.0	16.3	5.1	49.7	13.9	90.6
	17.8	16.9	4.7	44.9	15.6	90.4
	16.4	16.2	4.7	45.9	16.9	90.7
	24.2	16.3	4.5	42.4	12.7	88.9
	25.0	16.2	4.3	39.7	14.8	89.0
	11.1	13.0	4.2	49.0	22.7	92.0
Total	**18.9**	**16.9**	**4.6**	**44.7**	**14.9**	**90.0**

Total number of hours = 46669.7

HIGH TREATMENT GROUP

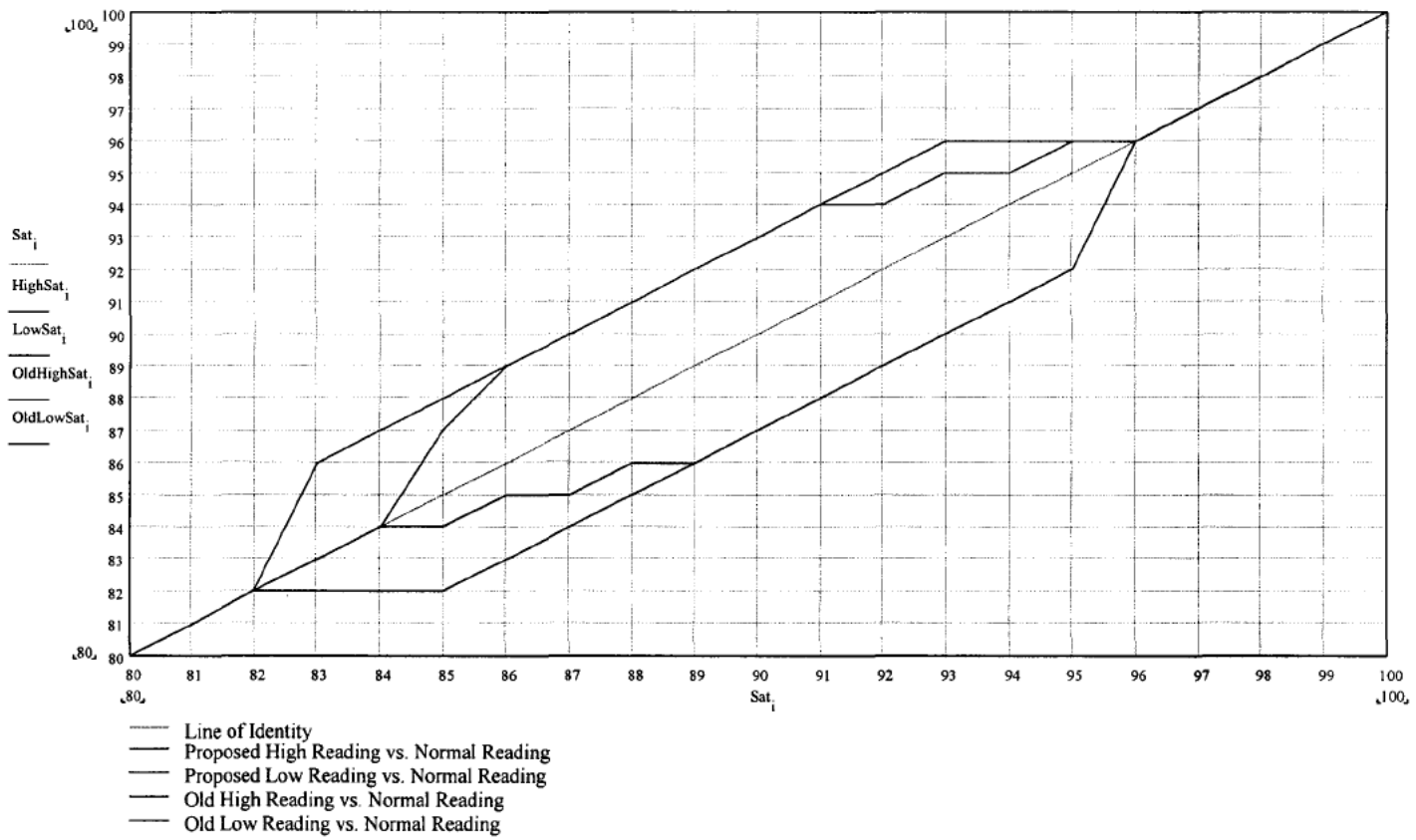
Center	<85	Low target 85-89	90	High target 91-95	>95	Mean O2 level
	9.1	12.1	3.1	37.9	38.0	92.3
	2.6	6.4	2.3	32.7	56.1	94.6
	3.2	6.0	1.9	31.6	57.3	95.0
	13.5	13.9	3.2	30.9	38.5	91.3
	10.7	14.1	3.9	44.4	26.8	91.2
	8.9	12.0	3.5	38.5	37.0	92.3
	9.3	14.1	4.0	46.3	26.4	91.4
	5.8	12.2	3.9	51.1	27.2	92.3
	5.2	13.1	4.1	47.3	30.6	92.6
	6.5	15.0	4.3	45.5	28.8	92.1
	7.0	11.4	3.3	39.0	39.2	92.7
	12.0	10.3	2.6	29.8	45.2	92.0
	10.9	15.6	5.1	52.2	16.2	90.2
	3.1	9.4	3.1	47.6	36.8	93.5
Total	**8.6**	**12.3**	**3.4**	**39.5**	**36.2**	**92.2**

Total number of hours = 58028.3

Data last updated 11/7/2005. Includes 153 infants.

Converting Actual Readings to Low and High Readings

Actual Reading	To Low Reading	To High Reading
100	100	100
99	99	99
98	98	98
97	97	97
96	96	96
95	92	96
94	91	96
93	90	96
92	89	95
91	88	94
90	87	93
89	86	92
88	85	91
87	84	90
86	83	89
85	82	88
84	82	87
83	82	86
82	82	82
81	81	81
80	80	80
etc	etc	etc



The Low, Actual & High Reading oximeters synchronize for values greater than or equal to 96 % and less than or equal to 82 %.

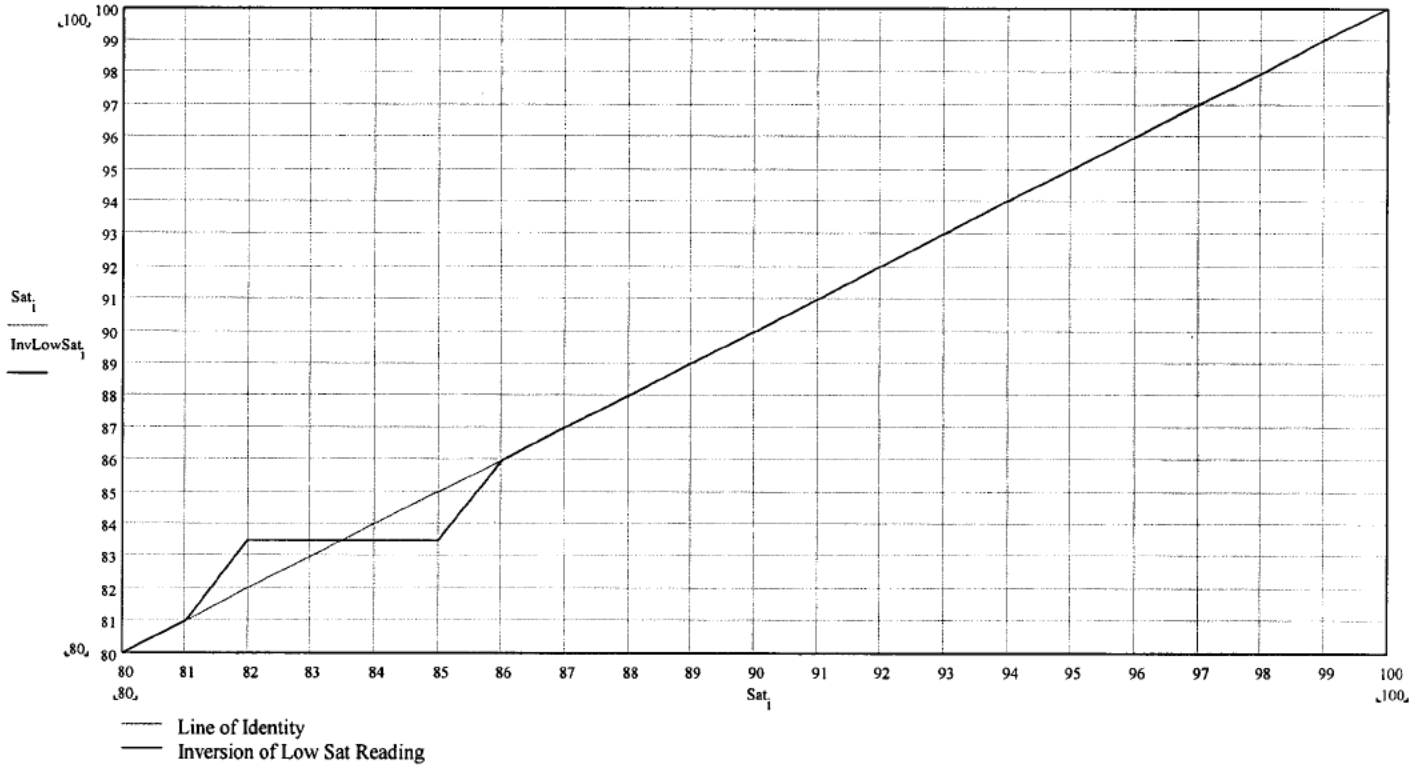
In the Actual range of 85 % to 95 %, the Low Reading Oximeter displays a value 3 points below actual.

In the Actual range of 83 % to 93 %, the High Reading Oximeter displays a value 3 points above actual

Converting Low Readings to Normal Readings

Low Reading	To Normal Reading
100	100
99	99
98	98
97	97
96	96
95	95.75
94	95.50
93	95.25
92	95
91	94
90	93
89	92
88	91
87	90
86	89
85	88
84	87
83	86
82	83.5
81	81
80	80
etc	etc

Applying the above inversion yields the following performance:

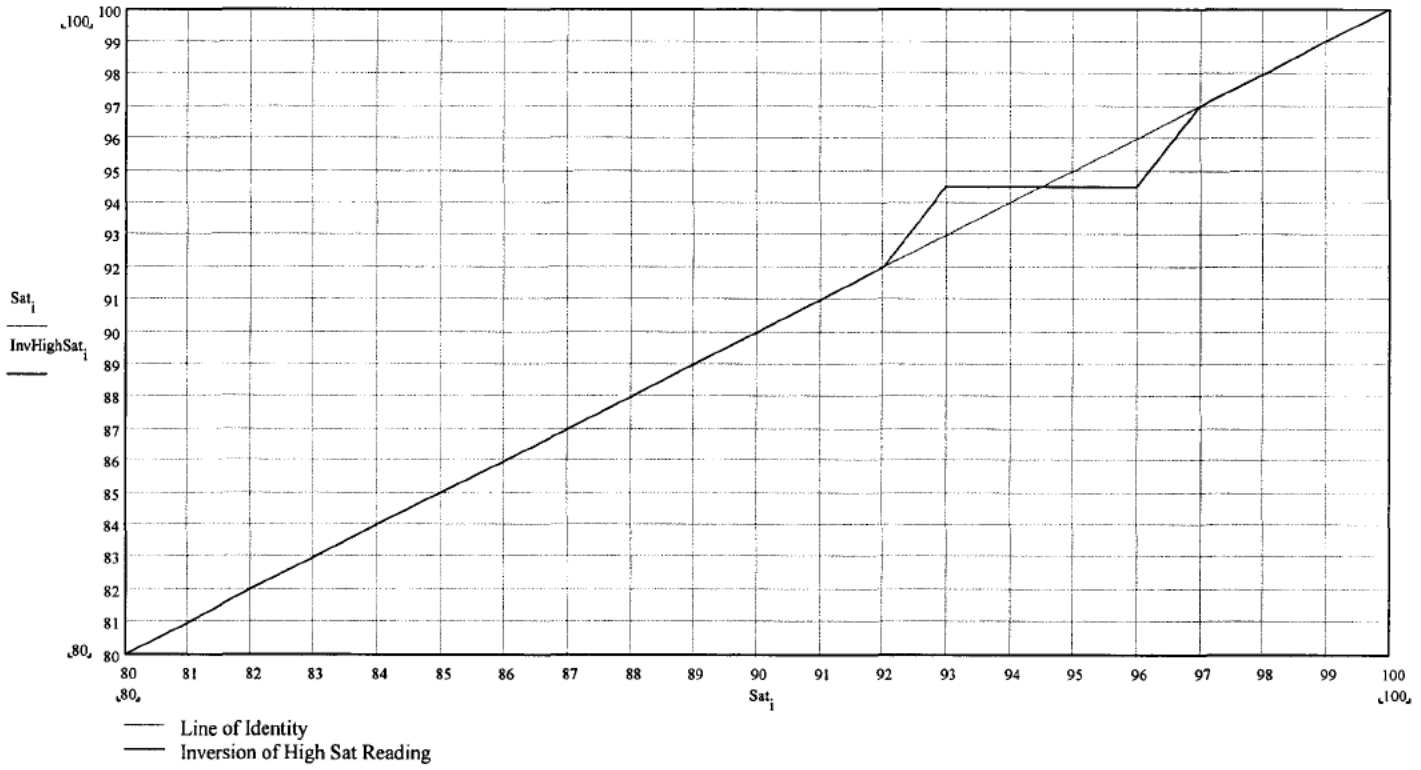


The inversion has no error above and below an actual reading of 86 % and 81 %, respectively. In between these limits, the inversion error does not exceed 1.5 %. Subjects are typically kept in the region of 91 % (88 % + 3 %) to 95 % (92 % + 3 %).

Converting High Readings to Actual Readings

High Reading	To Actual Reading
100	100
99	99
98	98
97	97
96	94.5
95	92
94	91
93	90
92	89
91	88
90	87
89	86
88	85
87	84.
86	83
85	82.75
84	82.50
83	82.25
82	82
81	81
80	80
etc	etc

Applying the above inversion yields the following performance:



The inversion has no error above and below an actual reading of 97 % and 92 %, respectively. In between these limits, the inversion error does not exceed 1.5 %. Subjects are typically kept in the region of 85 % (88 % - 3 %) to 89 % (92 % - 3 %).

From:	Neil Finer
To:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Cc:	Maynard.Rasmussen@sharp.com; "Neil Finer"
Date:	Monday, November 28, 2005 12:19:53 AM
Attachments:	Pct in each range (room air) 11-18-05.rtf DSMCMemotosites 11-22-05 adrev.doc Case Non Support data.xls Actual unmasked Pct in each O2 range 11-18-051.doc

---

Hello Everyone
In preparing for tomorrows call I thought we should have our strategy in front of us so that we alter it as needed.
Thanks for your suggestions
I have added the relevant attachments; these include the DSMC report, the data that the DSMC reviewed, the data for room air only, and Michele's data from Case.
In addition Michele sent data for 9 Non-SUPPORT infants with the SpO2 distribution:
To summarize the distribution:
> 95% sat - 56% (range 38-86)
90-95% sat - 26% (range 8-33%)
85-89% sat - 8% (range 2-13%)
< 85% sat - 11% (range 3-25%)
We also have the data from the Pilot that was done to test the algorithm separation performed at Sharp Mary Birch by Maynard.

20 recordings of ~24 hr each or ~500 hours of recording
Entry criteria identical to Support Trial
All infants on IMV or CPAP and Supplemental Oxygen
Sat alarms 84 and 96% with written orders and posted signs to keep SaO2 88-92%

Results from normal (non-skewed) Masimo oximeters:

<84%:	10% of time
84-87%:	10% of time
88-92%:	29% of time
93-96%:	40% of time
>96%:	9% of time

This is not directly comparable but shows considerable time with high SpO2. These ranges are not identical but consistent with Michele's data and the findings from the initial 153 SUPPORT infants

To review - The DSMC made the following 2 comments:

- There is a significant safety and exposure issue for the infants in the high saturation treatment group because an unacceptably high proportion of time was spent by these study subjects in the >95% range
- There is a futility concern for this arm of the trial in that there does not appear to be substantial separation between the two high and low saturation treatment groups, and the babies are not being kept in the target range the appropriate amount of time in order to meaningfully test the oxygen saturation intervention as originally designed.

Based on these two issues, the consensus of the Committee was to recommend stopping the oxygen saturation arms of the SUPPORT trial due to safety and futility concerns.

Other relevant data – in BOOST the infants in the higher SpO2 range had SpO2s> 95% for 90% of the

time. These were infants who were unable to maintain SpO2 > 94% in room air

In reviewing the DSMC comments I believe that our strategy moving forward should be as follows:

1. We should strenuously argue that the percent of time over 95% in NOT a safety issue as there is no antecedent data that such SpO2s for such a duration, ie 35% > 95% are toxic. We would argue that this duration is actually lower than may be expected.
2. We would additionally hope that an analysis will show excessive time at 96% which actually may represent values from 93% to 96%. This will also be true for the value of 84% which may be over-represented. This is a phenomenon of back converting the algorithm when trying to determine true SpO2 values from the altered oximeters. I have attached the actual skew as an attachment.
3. I would suggest that we change the low alarm to 80% and the high to 94%. This should push us toward the narrow targets
4. We need to develop increased in-service at all sites to encourage keeping infants in the narrower ranges of 88% to 92% - Signs at bedside, rewards by histogram results, and monthly recognition of the units with the best target data. Please suggest any mechanisms that you think would be effective
5. We need to rewrite the manual and protocol to clarify that we are aiming to produce different oxygen exposures using different SpO2 limits
6. I would suggest that we collect more FiO2 data. I would assume that all units keep hourly FiO2 data for all infants on ventilators and CPAP. I would propose that we collect hourly data for at least the first 14 days for all such infants and try to continue to collect such data for all infants who require oxygen via any mechanism. For prongs we would collect flow and and FiO2, and daily weight. We do have technology to continuously record FiO2. I will briefly discuss this – we could do this for the next 10-20 infants or more and compare with the SpO2 data. Please think about this.
7. I would fight vigorously to continue the trial as is, and re-evaluate the oximetry data after a further 100-200 infants
8. If we are forced to consider dropping the oximetry arm, then I would propose that we have all the Masimo oximeters converted to normal and continue to use them to collect the data about the actual SpO2 exposures of this population which will still be unique and incredibly useful in looking at durations of hyperoxia and hypoxia in the ELBW and their outcomes.
9. Other possibilities – redesign of the algorithm going below 85%, using a 3-5% SpO2 offset without correction for 1 arm, and standard oximeters for the other. I believe that Masimo was reluctant to design such an offset on the belief that clinicians would want to know the true SpO2 of an infant if below 85%.

Thanks for staying tuned. Talk to you in the morning.
Be well
Neil

HIGH TREATMENT GROUP: PERCENT OF TIME SPENT IN EACH O2 RANGE DAYS ON ROOM AIR*

LOW TREATMENT GROUP

Center Number	Total number of hours	<85	Low target 85-89	90	High target 91-95	>95	Mean O2 level
		2.8	4.1	1.6	37.7	53.7	95.6
		5.1	5.0	1.9	45.3	42.6	94.4
		6.5	7.2	2.5	42.6	41.2	94.3
		5.1	7.4	2.7	43.2	41.5	94.5
		3.0	4.9	1.8	46.7	43.6	95.0
		6.4	6.4	2.2	44.7	40.3	94.4
Total	**14193.2**	**4.5**	**5.5**	**2.0**	**42.0**	**46.1**	**94.8**

HIGH TREATMENT GROUP

Center Number	Total number of hours	<85	Low target 85-89	90	High target 91-95	>95	Mean O2 level
		1.3	4.5	1.8	27.0	65.4	95.9
		1.9	4.5	1.5	23.0	68.9	95.7
		2.9	4.3	1.4	23.8	67.6	95.4
		7.0	7.0	1.9	20.8	63.3	94.4
		1.0	3.7	1.5	28.4	65.4	95.6
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Total	**12414.1**	**2.9**	**4.5**	**1.5**	**22.5**	**68.8**	**95.6**

*Days on room air are defined as FiO2=0.21 or Mode of Support=7 (No Support) on SUPP05 or Oxygen=N or Highest Level of Support=7 (No Support) on SUPP11.

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DEPARTMENT OF HEALTH & HUMAN SERVICES National Institutes of Health

National Institute of Child Health and Human Development

November 22, 2005

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SUBJECT: Summary of the November 22, 2005 Data Safety and Monitoring Committee Conference Call

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cc: Rose Higgins
Alan Jobe
NICHD Neonatal Research Network PIs
NICHD Neonatal Research Network Coordinators
DSMC Members

Attachment

NEONATAL RESEARCH NETWORK

DATA SAFETY AND MONITORING COMMITTEE

DRAFT MINUTES

November 22, 1005

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After reviewing and discussing these data, the DSMC expressed significant concern about the following two issues:

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NOTE: Dr Dwyane Alexander, Director of NICHD, reviewed the above recommendation and discussed the specifics with Dr. Rose Higgins, Program Scientist for the Neonatal Research Network, and after thorough consideration of all of the issues, agreed with the recommendation and requested that enrollment be temporarily suspended into the trial until one can assure that the oxygen saturations are in the planned target range. Sites were notified on November 22, 2005 that enrollment should be temporarily suspended until further notice.

(b) (6)	<85	85-89	90-95	>95	total
	3.1	6.4	32.9	57.7	100.1
	4	4.5	19.3	72.3	100.1
	3.5	2.4	8.3	85.6	99.8
	19.3	12.2	29.2	39.3	100
	25.4	13.1	26.4	35.1	100
	18.52	11.9	30.7	38.9	100.02
	10.2	8.7	29.4	51.7	100
	8.7	7.9	29.2	54.2	100
	4.9	4.2	24.2	66.7	100
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sd	8.241578	3.87162	7.592504	16.91292	

PERCENT OF TIME SPENT IN EACH O2 RANGE
(DAYS ON SUPPLEMENTAL OXYGEN ONLY)

LOW TREATMENT GROUP

Center	<85	Low target 85-89	90	High target 91-95	>95	Mean O2 level
	13.5	11.6	3.5	51.8	19.4	91.5
	8.6	16.0	4.6	45.5	25.3	92.4
	12.5	5.4	1.7	70.0	10.4	91.6
	20.1	20.6	5.7	44.2	9.5	89.6
	18.2	16.2	4.7	47.5	13.3	90.0
	19.9	25.1	4.6	37.5	12.8	89.0
	21.0	18.8	5.3	42.2	12.6	89.0
	14.8	18.3	5.8	50.5	10.4	90.7
	15.0	16.3	5.1	49.7	13.9	90.6
	17.8	16.9	4.7	44.9	15.6	90.4
	16.4	16.2	4.7	45.9	16.9	90.7
	24.2	16.3	4.5	42.4	12.7	88.9
	25.0	16.2	4.3	39.7	14.8	89.0
	11.1	13.0	4.2	49.0	22.7	92.0
Total	**18.9**	**16.9**	**4.6**	**44.7**	**14.9**	**90.0**

Total number of hours = 46669.7

HIGH TREATMENT GROUP

Center	<85	Low target 85-89	90	High target 91-95	>95	Mean O2 level
	9.1	12.1	3.1	37.9	38.0	92.3
	2.6	6.4	2.3	32.7	56.1	94.6
	3.2	6.0	1.9	31.6	57.3	95.0
	13.5	13.9	3.2	30.9	38.5	91.3
	10.7	14.1	3.9	44.4	26.8	91.2
	8.9	12.0	3.5	38.5	37.0	92.3
	9.3	14.1	4.0	46.3	26.4	91.4
	5.8	12.2	3.9	51.1	27.2	92.3
	5.2	13.1	4.1	47.3	30.6	92.6
	6.5	15.0	4.3	45.5	28.8	92.1
	7.0	11.4	3.3	39.0	39.2	92.7
	12.0	10.3	2.6	29.8	45.2	92.0
	10.9	15.6	5.1	52.2	16.2	90.2
	3.1	9.4	3.1	47.6	36.8	93.5
Total	**8.6**	**12.3**	**3.4**	**39.5**	**36.2**	**92.2**

Total number of hours = 58028.3

Data last updated 11/7/2005. Includes 153 infants.

From: Raju, Tonse (NIH/NICHD)
To: "ccole@bidmc.harvard.edu"; "nfiner@ucsd.edu"; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT and US POST
Date: Friday, November 25, 2005 6:47:00 PM

I thought you may call today. But, I will be at work on Monday too. Feel free to call.
Tonse

Tonse N. K. Raju, MD
Program Scientist/Medical Officer
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD/National Institues of Health, Bethesda, MD
Phone: 240-631-8030; fax: 301-496-3790
Email: rajut@mail.nih.gov

Mailing address: 6100 Executive Blvd, Room 4B03
Bethesd, MD, 20892, USA,
(For overnight couriers: Rockville, MD, 20852)

From: ccole@bidmc.harvard.edu [mailto:ccole@bidmc.harvard.edu]
Sent: Tuesday, November 22, 2005 3:21 PM
To: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD)
Cc: Raju, Tonse (NIH/NICHD)
Subject: SUPPORT and US POST

Dear Neil and Rosemary (and Tonse),
First, I hope this finds each of you well.
The BIDMC CCI (i.e. IRB) reviewed the pilot randomized trial for US POST.
BIDMC CCI would like to contact either one or both of you regarding status of NICHD-Neo Research Network's SUPPORT and the saturation targets.
The issue relates to how IRBs of NICHD network centers viewed the risk to the participants.

BIDMC CCI asked if I viewed this study as greater than minimal risk to participants.
My response: 'Not above minimal risk.' Rationale: Since the overall range of both targets (SpO2 85-95%) was within the current range used by many NICUs, I did not view that this study was increasing the risk of an eligible patient beyond their usual care. There is insufficient evidence to claim any SpO2 targeted range as 'standard of care'. However, if there is a net benefit of one targeted zone compared to another, or a tradeoff in outcomes, then one of these targeted zones may increase the risk of certain patients for certain outcomes. So, I am requesting your permission to provide your contact information for a member of the BIDMC CCI to contact you.

I would also like to touch base with you. Realizing we are upon the holidays, I would like to speak with you before Wednesday mid-day if possible.
If not, let me know times that would be good to call you.

Thank you. I wish you a very Happy Thanksgiving. -
Cindy

Cynthia H. Cole, MD, MPH
Director of Research
Department of Neonatology

Beth Israel Deaconess Medical Center
330 Brookline Avenue, Boston, MA 02215
phone: 00+1+ 617-667-3276
FAX: 00+1+ 617-667-1742
email: ccole@bidmc.harvard.edu

From: Das, Abhik
To: Neil Finer; Wally Carlo, M.D.; Michele Walsh
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Donovan, Edward (DONOVAEF); Duara, Shahnaz; Rich, Wade; Newman, Nancy; Poole, W. Kenneth; Gantz, Marie; Schaefer, Scott E.
Subject: RE: re sat distribution data
Date: Friday, November 25, 2005 12:18:44 PM

Neil:

We are working on getting this done. However, I dont think we will have it in time for our call on Monday. As I understand it, the data dump from the pulse oximeters is so immense that a huge amount of data processing and compression has to be done at our end first before the data is an analyzable form. Currently we are in the process of re-programming that pre-processing component so that we can look at the data at the finer level that we need. Once our programmers get that done (they already started working on it on Wednesday, but RTI is closed Thurs/Friday for Thanksgiving), Marie will get you these numbers as soon as we can.

Thanks

Abhik

> -----Original Message-----
> **From:** Neil Finer [mailto:nfiner@ucsd.edu]
> **Sent:** Wednesday, November 23, 2005 10:18 PM
> **To:** 'Wally Carlo, M.D.'; Das, Abhik; 'Michele Walsh'
> **Cc:** 'Higgins, Rose'; 'Donovan, Edward (DONOVAEF)'; 'Duara, Shahnaz'; 'Rich, Wade'; 'Newman, Nancy'; Poole, W. Kenneth
> **Subject:** RE: re sat distribution data
>
> Wally
>
> I believe that this already being done as per my earlier email. Abhik can you confirm that you will be looking at each SpO2 value from 80% to 100% for the time spent at each value.
>
> Thanks
>
> Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2005 3:35 PM
To: Das, Abhik; Michele Walsh
Cc: Higgins, Rose; Finer, Neil; Donovan, Edward (DONOVAEF); Duara, Shahnaz; Rich, Wade; Newman, Nancy; Poole, W. Kenneth
Subject: RE: re sat distribution data

Maybe data of % of time in each sat %from 85 to 100 would be most helpful rather than data analyzed by ranges of sats.

What do you all think? Wally

From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, November 23, 2005 3:18 PM
To: Michele Walsh
Cc: Higgins, Rose; Finer, Neil; Donovan, Edward (DONOVAEF); Wally Carlo, M.D.; Duara, Shahnaz; Rich, Wade; Newman, Nancy; Poole, W. Kenneth
Subject: RE: re sat distribution data

I forgot to add a bit of background here. In August, with prodding from Neil and Wally we approached the DSMC with the subcommittee's request to periodically monitor the sat data by treatment group to ensure that sufficient separation was being achieved (see table below). The DSMC decided that any such monitoring should be done by it, and not the study investigators. It was in this spirit that this data was then shown to the DSMC. We sent them the data in September, but it took a while to find a time for all of them to meet. However, the pattern we saw in September was virtually identical to what we see now (in the tables you have).

Thanks

Abhik

Data	High Saturation	Low Saturation
% of time in range 85-89%		
% of time in range 90%		
% of time in range 91-95		
% of time below range (= 84%)		
% of time above range (= 96%)		
Average Saturation		
Minimum Saturation		
Maximum Saturation		

-----Original Message-----
From: Das, Abhik
Sent: Wednesday, November 23, 2005 4:05 PM
To: 'Michele Walsh'
Cc: Higgins, Rose; Finer, Neil; Donovan, Edward (DONOVAEF); Carlo, Wally; Duara, Shahnaz; Rich, Wade; Newman, Nancy; Poole, W. Kenneth
Subject: RE: re sat distribution data

I think Ken's original intent in sending this to the DSMC was primarily a futility concern about inadequate separation -- kids in the low sat arm were in fact in the high target group more often (45% time) than kids in the high sat arm (39%). That could not be shown in a masked

way. In any case, in my experience DSMC's rarely buy this masking business -- if we mask they just come back and ask us to unmask them.

Thanks

Abhik

-----Original Message-----
From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Wednesday, November 23, 2005 3:54 PM
To: Das, Abhik
Cc: Higgins, Rose; Finer, Neil; Donovan, Edward (DONOVAEF); Carlo, Wally; Duara, Shahnaz; Rich, Wade; Newman, Nancy
Subject: Re: re sat distribution data

Abhik: Why were these not masked by group as would ordinarily be done- Group A vs Group B? Michele

----- Original Message -----
From: Das, Abhik
To: Michele Walsh ; Neil Finer ; Edward Donovan ; Higgins, Rosemary (NIH/NICHD) ; nfiner@ucsd.edu
Cc: Wade Rich ; MD' 'Maynard Rasmussen ; Poole, W. Kenneth ; Hastings, Betty J. ; Michele ; M.D.' 'Avroy A. Fanaroff ; Wally Carlo ; Shahnaz Duara ; Gantz, Marie
Sent: Wednesday, November 23, 2005 3:43 PM
Subject: RE: re sat distribution data

All they saw was the table that Betty sent out earlier today along with the DSMC memo.

Thanks

Abhik

-----Original Message-----
From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Wednesday, November 23, 2005 3:35 PM
To: Neil Finer; 'Edward Donovan'; 'Higgins, Rosemary (NIH/NICHD)'; nfiner@ucsd.edu
Cc: Das, Abhik; Wade Rich; 'MD' 'Maynard Rasmussen'; Poole, W. Kenneth; Hastings, Betty J.; 'Michele'; 'M.D.' 'Avroy A. Fanaroff'; 'Wally Carlo'; 'Shahnaz Duara'
Subject: Re: re sat distribution data

I agree with all of Neils comments! Did the DSMC see if the FiO2 was different which was the intent?
Michele

----- Original Message -----
From: Neil Finer
To: 'Higgins, Rosemary (NIH/NICHD)' ; 'Edward Donovan' ; 'Michele Walsh' ; Neil Finer
Cc: 'Shahnaz Duara' ; 'Wally Carlo' ; 'M.D.' 'Avroy A. Fanaroff' ; 'Michele' ; 'Betty Hastings' ; 'Ken Poole' ; 'MD' 'Maynard Rasmussen' ; Wade Rich
Sent: Wednesday, November 23, 2005 3:30 PM
Subject: RE: re sat distribution data

Hello All

I agree with Ed's comments. In fact we wanted to create different oxygen exposures and the way to do this was to have different periods of time at different SpO2 levels, and it would appear that we have succeeded.

I am also uncertain why non blinded data was evaluated. Our previous comments were that some units were experiencing that the high alarms were not being set. We did not postulate that this was an issue for one or other arm of the trial, but rather a response to frequent alarms. It is the alarms that work to keep the babies in range.

Also we need to understand that the design of the algorithms was also to push the infants into the middle range. I will try to explain this. For an infant whose oximeter displays 88% to 92% when the actual SpO2 is 91% to 95%, as the true, SpO2 increases toward 95%, the display will increase to 95% to 96% and the alarm can be activated (with the appropriate time delay etc) at actual values of 94-95%. Thus this infant will alarm when the actual SpO2 is BELOW the upper limit of 95%. This will tend to keep the infant more within the desired target range. The same will happen for infants in the lower range, in that when their actual SpO2 is 87%, the display will show 85% and any further decrease will trigger the alarm.

In reviewing the DSMC comments I believe that our strategy moving forward should be as follows:

1. We should strenuously argue that the percent of time over 95% in NOT a safety issue as there is no antecedent data that such SpO2s for such a duration, ie 35% > 95% are toxic. We would argue that this duration is actually lower than may be expected.
2. We would additionally hope that an analysis will show excessive time at 96% which actually may represent values from 93% to 96%
3. I would suggest that we change the low alarm to 80% and the high to 94%. This should push us toward the narrow targets
4. We need to rewrite the manual and protocol to clarify that we are aiming to produce different oxygen exposures using different SpO2 limits
5. I would fight vigorously to continue the trial as is, and re-evaluate the oximetry data after a further 100-200 infants
6. If we are forced to consider dropping the oximetry arm, then have all the Masimo oximeters converted to normal and continue to use them to collect the data about the actual SpO2 exposures of this population which will still be unique and incredibly useful in looking at durations of hyperoxia and hypoxia in the ELBW and their outcomes.

Please consider these suggestions and let me know your thoughts and suggestions

I would like to be prepared for our Monday call.

Have a great Thanksgiving

Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 23, 2005 6:48 AM
To: Edward Donovan; Michele Walsh; Neil Finer
Cc: Shahnaz Duara; Wally Carlo; M.D.' 'Avroy A. Fanaroff; Michele; Betty Hastings; Ken Poole; MD' 'Maynard Rasmussen; Wade Rich
Subject: RE: re sat distribution data

Betty will send it out within the next hour.

Thanks
Rose

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Wednesday, November 23, 2005 9:46 AM
To: 'Michele Walsh'; Higgins, Rosemary (NIH/NICHD); Neil Finer
Cc: 'Shahnaz Duara'; 'Wally Carlo'; M.D.' 'Avroy A. Fanaroff; 'Michele'; 'Betty Hastings'; 'Ken Poole'; MD' 'Maynard Rasmussen; 'Wade Rich'
Subject: RE: re sat distribution data

Do we have any details on this issue?
What I understand is that there is a concern about exposure to high O2 sat disproportionately in one arm? If it's the "high" arm, then this is the purpose of the study, i.e. to see if decreasing oxygen exposure reduces BPD and ROP. Am I missing the boat? When are we going to see the actual concerns of the DSMC?

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0180
Fax 513-636-0171
www.cincinnatichildrens.org/cprc

>>> "Neil Finer" <nfiner@ucsd.edu> 11/22/2005 6:30:43 PM >>>

Hi Michele and all
I have reviewed Abbot's abstract and he found that the SpO2 was > 95% for

about 17% of the time.
In addition the skew for correcting the stored values in the oximeter back to real unaltered values is such that for the group in high range ie 88% to 92% is actually 91% to 95%, in the process of correcting, there are a number
of real, actual SpO2 values - 93%, 94%, 95% and 96% which are all converted
to a display value of 96% because of rounding of decimal points (The Masimo
cannot display decimals and we had agreed to this formula as 96% cannot be
linked to 4 different actual SpO2 values).
We were aware of this, and used this because we wished to maintain the separation over the widest range. This will represent a problem in reviewing
the unskewed data in that there will be an over-representation of values at 96% for the high range infants and 85% for the low range infants.
RTI in converting the data back to "normal" will only see a 96% value for any value of 93%, 94% or 95% or 96% in the 91-95% target infants, and thus
we will find a much increased percentage for the actual value of 96% after data conversion, as was done.
We therefore need to look at the value of 96% separately, as we do for 85%
We need to understand that values of 96% after conversion will represent actual values of anywhere from 93 to 96%.
However we had agreed that this would not be realistic so that fractions were assigned most of which if corrected to a full integer would read 96%.

This now raises the issue of the study intent and design. We did not design
the trial to produce different SpO2s but rather to use the SpO2 to create different oxygen exposures. To my knowledge we did not analyze the FiO2 for
the 2 groups. In addition we do not know at present if the % of time > 95%
and < 85% are different than what is normally experienced for ELBW infants.
We need to know the percentage of time at the single value of 96% and probably similarly at 85%. Some values of 96% will actually represent values
that should be within the 92% to 95% range, but we will have no ability to know this.
I believe that if we achieve close to 60% within 85% to 95% with the current
skews, that we will achieve FiO2 differences.
STOP ROP kept the high range infants at > 95% for > 90% of the time. I am
uncertain as to the known risk of any value for SpO2 > 95% below 90%.
I also believe that we may increase our time in the narrow and broader ranges by lowering the low alarm to 80% and the high alarm to 94%.
Lets think all of this over.
Rose, can you ask Marie Ganz to provide us the actual percentage of time in
the various ranges for all of the infants (non corrected data) for the time only in room air. She previously gave us in oxygen and overall. The room air
only will provide a ranges of SpO2 > 95% and we can look at this in interpreting the percent time > 96%.

I believe that we can probably move ahead with the trial and I am prepared
to argue for this.
In spite of this, have a peaceful and restful Thanksgiving
Neil

-----Original Message-----
From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Tuesday, November 22, 2005 1:52 PM
To: Laptook, Abbot; Finer, Neil; Higgins, Rose
Subject: re sat distribution data

Hi Rose:
Another thought about sat distribution data. We have Abbot's study at Dallas that looks at distribution of sats as well. Perhaps we can look at this as well.
I will let you know about the Case non Support data.
Michele

From:	Edward Donovan
To:	WCarlo@peds.uab.edu; nfiner@pedsmail.ucsd.edu; nfiner@ucsd.edu
Cc:	mcw3@case.edu; Higgins, Rosemary (NIH/NICHD) [E]; sduara@miami.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu; bkh@rti.org; poo@rti.org; Maynard.Rasmussen@sharp.com; wrich@ucsd.edu
Subject:	RE: re sat distribution data
Date:	Friday, November 25, 2005 9:46:48 AM

I am in agreement with Neil's proposals.

Edward F. Donovan, M.D.
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>>> "Neil Finer" <nfiner@ucsd.edu> 11/24/05 9:51 PM >>>
Hi Wally

The Poets study demonstrated compliance for a range of SpO2 from 87% to 96%.
We don't know our percentage of time in this range. We will have more knowledge when we see the individual SpO2 data and even then because the values of 85% and 96% will be overrepresented, I am not sure that we will
get all the answers.

I think that a 5% range is probably too small to hit with regularity in the
majority of NICUs without a dedicated person doing nothing else. We could
widen this maximal separation if we change the skew to go below 85%. We were
reluctant to go there before. There is really no new data to indicate that
going lower is safer. In fact, there is essentially no data as large as the
study database for true SpO2 values of 84% and less and 96% and greater.
This study will provide the data as to whether any duration below or above
these values is beneficial or harmful. I would like to push for lowering the
alarm limits.

Another paradoxical thought as suggested by Maynard is that we decrease the
averaging and alarm delays, so that the care teams are more quickly informed
when infants go out of the narrow target range.

I am also not sure that we haven't created to different oxygen exposures.

The two randomized groups of infants differ by 10% for the percent of time
below 85%. This could be associated with a difference in oxygen exposure. In
addition this difference could drive different outcomes which is exactly what we want to test.

However we only collect these values 3 times per day. We do have technology
to collect the FiO2 continuously and we use this for some of our DR research. Should we try to do this for 10-20 infants in each range?

I will keep thinking on this till we talk on Monday

Hope you all had a great day

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2005 8:20 PM
To: Neil Finer; Neil Finer
Cc: Michele Walsh; MD' 'Maynard Rasmussen; Avroy A. Fanaroff, M.D.; Betty
Hastings; Ed Donovan; higginsr@mail.nih.gov; Ken Poole; Michele; Shahnaz Duara; Wade Rich
Subject: RE: re sat distribution data

In Poets study, it was a bedside person who achieved the same performance as
the servo control. wally

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 23, 2005 9:18 PM
To: Wally Carlo, M.D.; Neil Finer
Cc: 'Michele Walsh'; 'MD' 'Maynard Rasmussen'; 'Avroy A. Fanaroff, M.D.';
'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole';
'Michele'; 'Shahnaz Duara'; 'Wade Rich'
Subject: RE: re sat distribution data

Thanks Wally

Would this be someone at the bedside or a person to assist with reviewing
the monitor ranges etc. One concern that I have would be the reproducibility
of using such an individual. While a number of studies have shown the

value
of servo control - most recently Poets study, It is doubtful that a manufacturer will develop such a device in view of the potential liability.

Let's keep thinking about other options

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2005 1:28 PM
To: Neil Finer
Cc: Michele Walsh; MD' 'Maynard Rasmussen; Avroy A. Fanaroff, M.D.; Betty
Hastings; Ed Donovan; higginsr@mail.nih.gov; Ken Poole; Michele; Neil Finer;
Shahnaz Duara; Wade Rich
Subject: RE: re sat distribution data

Neil:

A recent study of pulse oximetry by servocontrol or dedicated person showed
extremely high compliance with the saturation targets. I believe it was 80-90%. I think we should consider adding resources to have a dedicated person achieve high compliance.

Wally

From: Neil Finer [mailto:nfiner@pedsmail.ucsd.edu]
Sent: Wednesday, November 23, 2005 2:57 PM
To: Wally Carlo, M.D.
Cc: Michele Walsh; MD' 'Maynard Rasmussen; Avroy A. Fanaroff, M.D.; Betty
Hastings; Ed Donovan; higginsr@mail.nih.gov; Ken Poole; Michele; Neil Finer;
Shahnaz Duara; Wade Rich
Subject: RE: re sat distribution data

Wally

Do you have any suggestions for helping to keep us in the narrower target

levels? Another option is a redesign of the oximeters, or a simple shift of
3-5% for all values as in BOOST. This may produce better separation throughout, but is problematic at the high ranges.

With regards to great clinical care, we do not have any data as to the ideal
SpO2 ranges that we should target. No such data has ever been collected and
this was an aim of this trial. We need the ranges to be tested with the relevant outcomes, but I agree with the DSMC that we also need separation.

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2005 12:48 PM
To: Neil Finer; Higgins, Rosemary (NIH/NICHD); Edward Donovan; Michele Walsh; Neil Finer
Cc: Shahnaz Duara; M.D.' 'Avroy A. Fanaroff; Michele; Betty Hastings; Ken
Poole; MD' 'Maynard Rasmussen; Wade Rich
Subject: RE: re sat distribution data

Hi:

I think it is important that everyone is aware of usual sats in NICUs. Michele's data is helpful. The multicenter study I mentioned yesterday is
also helpful. Nonetheless, we should strive to provide great clinical care,
not just do great trials.

I agree that we want different O2 exposures but we must remember that in part, that differential exposure is best accomplished while the infants are
at a saturation 88-92%. I like Neil's idea of lower alarm levels but I suspect, it will reduce but not eliminate the problem.

I think it is important to compare our data with that of other trials such
as the BOOST one, which also show a high frequency of sats >95%.

Wally

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 23, 2005 2:30 PM
To: 'Higgins, Rosemary (NIH/NICHD)'; 'Edward Donovan'; 'Michele Walsh'; Neil
Finer
Cc: 'Shahnaz Duara'; Wally Carlo, M.D.; 'M.D.' 'Avroy A. Fanaroff'; 'Michele'; 'Betty Hastings'; 'Ken Poole'; 'MD' 'Maynard Rasmussen'; Wade Rich
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From: Michele Walsh [mailto:mcw3@case.edu] <mailto:mcw3@case.edu%5d>
Sent: Tuesday, November 22, 2005 1:52 PM
To: Laptook, Abbot; Finer, Neil; Higgins, Rose
Subject: re sat distribution data

Hi Rose:
Another thought about sat distribution data. We have Abbot's study at Dallas that looks at distribution of sats as well. Perhaps we can look at
this as well.
I will let you know about the Case non Support data.
Michele

From: Neil Finer
To: "Wally Carlo, M.D."; Neil Finer
Cc: mcw3@case.edu; Maynard.Rasmussen@sharp.com; AAF2@po.cwru.edu; bkh@rti.org; Edward.Donovan@chmcc.org; Higgins, Rosemary (NIH/NICHD) [E]; poo@rti.org; mcw3@po.cwru.edu; sduara@miami.edu; wrich@ucsd.edu
Subject: RE: re sat distribution data
Date: Friday, November 25, 2005 12:08:47 AM

Wally
I agree with the goal of better SpO2 control but at present we don't know the ideal range – this makes any change in the study difficult apart from more education and better attention to alarms. Do you think we should change the alarm limit as previously suggested – 80% to 94%??
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, November 24, 2005 7:05 PM
To: nfiner@ucsd.edu; nfiner@pedsmail.ucsd.edu
Cc: mcw3@case.edu; Maynard.Rasmussen@sharp.com; AAF2@po.cwru.edu; bkh@rti.org; Edward.Donovan@chmcc.org; higginsr@mail.nih.gov; poo@rti.org; mcw3@po.cwru.edu; sduara@miami.edu; wrich@ucsd.edu
Subject: Re: re sat distribution data

Neil:
The compliance in the Poets paper was better even when you look only at the clinical nurse. I think we must be sure we are doing the best trial possible. I think that in the future there will be O2 servocontrol systems in place. In the meantime, we could train clinicians in many clinical and physiological aspects of O2 sats such as importance of targets, baseline sats vs expected desats, etc

I think we should strongly endorse continuation of the trial but also need to consider specific improvements. I want to try more education of the bedside staff, closer supervision by the nuring leadership, help from RTs, and others.

Wally
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Neil Finer <nfiner@pedsmail.ucsd.edu>
CC: 'Michele Walsh' <mcw3@case.edu>; 'MD' 'Maynard Rasmussen' <Maynard.Rasmussen@sharp.com>; 'Avroy A. Fanaroff, M.D.' <aaf2@po.cwru.edu>; 'Betty Hastings' <bkh@rti.org>; 'Ed Donovan' <Edward.Donovan@chmcc.org>; higginsr@mail.nih.gov <higginsr@mail.nih.gov>; 'Ken Poole' <poo@rti.org>; 'Michele' <mcw3@po.cwru.edu>; 'Shahnaz Duara' <sduara@miami.edu>; 'Wade Rich' <wrich@ucsd.edu>
Sent: Thu Nov 24 20:51:35 2005
Subject: RE: re sat distribution data

Hi Wally

The Poets study demonstrated compliance for a range of SpO2 from 87% to 96%. We don't know our percentage of time in this range. We will have more knowledge when we see the individual SpO2 data and even then because the values of 85% and 96% will be overrepresented, I am not sure that we will get all the answers.

I think that a 5% range is probably too small to hit with regularity in the majority of NICUs without a dedicated person doing nothing else. We could widen this maximal separation if we change the skew to go below 85%. We

were reluctant to go there before. There is really no new data to indicate that going lower is safer. In fact, there is essentially no data as large as the study database for true SpO2 values of 84% and less and 96% and greater. This study will provide the data as to whether any duration below or above these values is beneficial or harmful. I would like to push for lowering the alarm limits.

Another paradoxical thought as suggested by Maynard is that we decrease the averaging and alarm delays, so that the care teams are more quickly informed when infants go out of the narrow target range.

I am also not sure that we haven't created to different oxygen exposures. The two randomized groups of infants differ by 10% for the percent of time below 85%. This could be associated with a difference in oxygen exposure. In addition this difference could drive different outcomes which is exactly what we want to test.

However we only collect these values 3 times per day. We do have technology to collect the FiO2 continuously and we use this for some of our DR research. Should we try to do this for 10-20 infants in each range?

I will keep thinking on this till we talk on Monday

Hope you all had a great day

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2005 8:20 PM
To: Neil Finer; Neil Finer
Cc: Michele Walsh; MD' 'Maynard Rasmussen; Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; higginsr@mail.nih.gov; Ken Poole; Michele; Shahnaz Duara; Wade Rich
Subject: RE: re sat distribution data

In Poets study, it was a bedside person who achieved the same performance as the servo control. wally

---

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 23, 2005 9:18 PM
To: Wally Carlo, M.D.; Neil Finer
Cc: 'Michele Walsh'; 'MD' 'Maynard Rasmussen'; 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Shahnaz Duara'; 'Wade Rich'
Subject: RE: re sat distribution data

Thanks Wally

Would this be someone at the bedside or a person to assist with reviewing the monitor ranges etc. One concern that I have would be the reproducibility of using such an individual. While a number of studies have shown the value of servo control – most recently Poets study, It is doubtful that a manufacturer will develop such a device in view of the potential liability.

Let's keep thinking about other options

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2005 1:28 PM
To: Neil Finer
Cc: Michele Walsh; MD' 'Maynard Rasmussen; Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; higginsr@mail.nih.gov; Ken Poole; Michele; Neil Finer; Shahnaz Duara; Wade Rich
Subject: RE: re sat distribution data

Neil:

A recent study of pulse oximetry by servocontrol or dedicated person showed extremely high compliance with the saturation targets. I believe it was 80-90%. I think we should consider adding resources to have a dedicated person achieve high compliance.

Wally

From: Neil Finer [mailto:nfiner@pedsmail.ucsd.edu]
Sent: Wednesday, November 23, 2005 2:57 PM
To: Wally Carlo, M.D.
Cc: Michele Walsh; MD' 'Maynard Rasmussen; Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; higginsr@mail.nih.gov; Ken Poole; Michele; Neil Finer; Shahnaz Duara; Wade Rich
Subject: RE: re sat distribution data

Wally

Do you have any suggestions for helping to keep us in the narrower target levels? Another option is a redesign of the oximeters, or a simple shift of 3-5% for all values as in BOOST. This may produce better separation throughout, but is problematic at the high ranges.

With regards to great clinical care, we do not have any data as to the ideal SpO2 ranges that we should target. No such data has ever been collected and this was an aim of this trial. We need the ranges to be tested with the relevant outcomes, but I agree with the DSMC that we also need separation.

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2005 12:48 PM
To: Neil Finer; Higgins, Rosemary (NIH/NICHD); Edward Donovan; Michele Walsh; Neil Finer
Cc: Shahnaz Duara; M.D.' 'Avroy A. Fanaroff; Michele; Betty Hastings; Ken Poole; MD' 'Maynard Rasmussen;

Wade Rich
Subject: RE: re sat distribution data

Hi:

I think it is important that everyone is aware of usual sats in NICUs. Michele's data is helpful. The multicenter study I mentioned yesterday is also helpful. Nonetheless, we should strive to provide great clinical care, not just do great trials.

I agree that we want different O2 exposures but we must remember that in part, that differential exposure is best accomplished while the infants are at a saturation 88-92%. I like Neil's idea of lower alarm levels but I suspect, it will reduce but not eliminate the problem.

I think it is important to compare our data with that of other trials such as the BOOST one, which also show a high frequency of sats >95%.

Wally

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 23, 2005 2:30 PM
To: 'Higgins, Rosemary (NIH/NICHD)'; 'Edward Donovan'; 'Michele Walsh'; Neil Finer
Cc: 'Shahnaz Duara'; Wally Carlo, M.D.; 'M.D.' 'Avroy A. Fanaroff'; 'Michele'; 'Betty Hastings'; 'Ken Poole'; 'MD' 'Maynard Rasmussen'; Wade Rich
Subject: RE: re sat distribution data

Hello All

I agree with Ed's comments. In fact we wanted to create different oxygen exposures and the way to do this was to have different periods of time at different SpO2 levels, and it would appear that we have succeeded.

I am also uncertain why non blinded data was evaluated. Our previous comments were that some units were experiencing that the high alarms were not being set. We did not postulate that this was an issue for one or other arm of the trial, but rather a response to frequent alarms. It is the alarms that work to keep the babies in range.

Also we need to understand that the design of the algorithms was also to push the infants into the middle range. I will try to explain this. For an infant whose oximeter displays 88% to 92% when the actual SpO2 is 91% to 95%, as the true, SpO2 increases toward 95%, the display will increase to 95% to 96% and the alarm can be activated (with the appropriate time delay etc) at actual values of 94-95%. Thus this infant will alarm when the actual SpO2 is BELOW the upper limit of 95%. This will tend to keep the infant more within the desired target range. The same will happen for infants in the lower range, in that when their actual SpO2 is 87%, the display will show 85% and any further decrease will trigger the alarm.

In reviewing the DSMC comments I believe that our strategy moving forward should be as follows:

1. We should strenuously argue that the percent of time over 95% in NOT a safety issue as there is no antecedent

data that such SpO2s for such a duration, ie 35% > 95% are toxic. We would argue that this duration is actually lower than may be expected.

2. We would additionally hope that an analysis will show excessive time at 96% which actually may represent values from 93% to 96%
3. I would suggest that we change the low alarm to 80% and the high to 94%. This should push us toward the narrow targets
4. We need to rewrite the manual and protocol to clarify that we are aiming to produce different oxygen exposures using different SpO2 limits
5. I would fight vigorously to continue the trial as is, and re-evaluate the oximetry data after a further 100-200 infants
6. If we are forced to consider dropping the oximetry arm, then have all the Masimo oximeters converted to normal and continue to use them to collect the data about the actual SpO2 exposures of this population which will still be unique and incredibly useful in looking at durations of hyperoxia and hypoxia in the ELBW and their outcomes.

Please consider these suggestions and let me know your thoughts and suggestions

I would like to be prepared for our Monday call.

Have a great Thanksgiving

Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 23, 2005 6:48 AM
To: Edward Donovan; Michele Walsh; Neil Finer
Cc: Shahnaz Duara; Wally Carlo; M.D.' 'Avroy A. Fanaroff; Michele; Betty Hastings; Ken Poole; MD' 'Maynard Rasmussen; Wade Rich
Subject: RE: re sat distribution data

Betty will send it out within the next hour.

Thanks
Rose

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Wednesday, November 23, 2005 9:46 AM
To: 'Michele Walsh'; Higgins, Rosemary (NIH/NICHD); Neil Finer
Cc: 'Shahnaz Duara'; 'Wally Carlo'; M.D.' 'Avroy A. Fanaroff; 'Michele'; 'Betty Hastings'; 'Ken Poole'; MD' 'Maynard Rasmussen; 'Wade Rich'
Subject: RE: re sat distribution data

know this.
I believe that if we achieve close to 60% within 85% to 95% with the current skews, that we will achieve FiO2 differences.
STOP ROP kept the high range infants at > 95% for > 90% of the time. I am uncertain as to the known risk of any value for SpO2 > 95% below 90%.
I also believe that we may increase our time in the narrow and broader ranges by lowering the low alarm to 80% and the high alarm to 94%.
Lets think all of this over.
Rose, can you ask Marie Ganz to provide us the actual percentage of time in the various ranges for all of the infants (non corrected data) for the time only in room air. She previously gave us in oxygen and overall. The room air only will provide a ranges of SpO2 > 95% and we can look at this in interpreting the percent time > 96%.

I believe that we can probably move ahead with the trial and I am prepared to argue for this.
In spite of this, have a peaceful and restful Thanksgiving
Neil

-----Original Message-----
From: Michele Walsh [mailto:mcw3@case.edu] <mailto:mcw3@case.edu%5d>
Sent: Tuesday, November 22, 2005 1:52 PM
To: Laptook, Abbot; Finer, Neil; Higgins, Rose
Subject: re sat distribution data

Hi Rose:
Another thought about sat distribution data. We have Abbot's study at Dallas that looks at distribution of sats as well. Perhaps we can look at this as well.
I will let you know about the Case non Support data.
Michele

From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT conference call
Date: Thursday, November 24, 2005 1:40:12 PM
Importance: High

Rose
when I talked to you, I was so exhausted I forgot to ask why the DSMB wanted it stopped---only because of lack of separation of 2 oxygen saturation levels?
Have a wonderful Thanksgiving---take it easy on the turkey and football
Thanks
Seetha

-----Original Message-----
From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Wednesday, November 23, 2005 9:59 AM
To: poo@rti.org; barbara_stoll@oz.ped.emory.edu; Charles.Rosenfeld@UTSouthwestern.edu; dale_phelps@urmc.rochester.edu; Das, Abhik; dstevenson@stanford.edu; edward.donovan@chmcc.org; goldb008@mc.duke.edu; higginsr@mail.nih.gov; jlemons@iupui.edu; Jobea0@chmcc.org; jon.e.tyson@uth.tmc.edu; alaptook@WIHRI.org; mcw3@cwru.edu; moshea@wfubmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; sduara@miami.edu; Shankaran, Seetha; wcarlo@peds.uab.edu; WOh@WIHRI.org
Cc: Alice.J.Reardon@uth.tmc.edu; aellison@med.miami.edu; echaisso@iupui.edu; (b) (6) diane.timmer@cchmc.org; fmartinez@ucsd.edu; Karen.Kirby@UTSouthwestern.edu; debra.camputaro@yale.edu; Townsend, Katrice; KGilley@CareNE.org; lisa.joo@stanford.edu; msumner@peds.uab.edu; mazie_tinsley@oz.ped.emory.edu; renee.dunbar-scott@oz.ped.emory.edu; Jensen, Rosemary; gonza025@mc.duke.edu; Wendy Holcomb; Hastings, Betty J.; Zaterka-Baxter, Kristin; Petrie, Carolyn; Gantz, Marie; wrich@ucsd.edu
Subject: SUPPORT conference call
Importance: High

Please send your availably for this urgent and important conference call regarding the SUPPORT trial. I will schedule a SUPPORT subcommittee call first (Mon or Tues) and then a second call with the NRN PIs (Wed or Thurs).

If you are unable, please send the availability for the Alt-PI or trial PI at the site.

Mon Nov 28
Tues Nov 29
Wed Dec 1
Thurs Dec 2

Thank you!

Carolyn Petrie Huitema
Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 902
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Wally Carlo, M.D.
To: Das, Abhik; Duara, Shahnaz; Michele Walsh; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Donovan, Edward (DONOVAEF); Rich, Wade; Newman, Nancy
Cc: Gantz, Marie; Poole, W. Kenneth
Subject: RE: RBC Non SUPPORT Saturation Data
Date: Wednesday, November 23, 2005 4:39:41 PM

Abhik: Could we get the table with the ranges of saturations with the cut-off 88-92 as well? Wally

---

From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, November 23, 2005 10:57 AM
To: Duara, Shahnaz; Michele Walsh; Higgins, Rose; Finer, Neil; Donovan, Edward (DONOVAEF); Wally Carlo, M.D.; Rich, Wade; Newman, Nancy
Cc: Gantz, Marie; Poole, W. Kenneth
Subject: RE: RBC Non SUPPORT Saturation Data

The hours reported in the tables that the DSMC saw (and which you have now been sent) are for days on supplemental O2 only; so we have taken out days the infants are on room air (defined as FiO2=0.21 or Mode of Support=7 (No Support) as per SUPP05 or Oxygen=N or Highest Level of Support=7 (No Support) as per SUPP11). However, it is possible that there are times on the supplemental O2 days that the babies are actually on room air; but we have tried to exclude time on room air from the tables that the DSMC saw as best we could.

Thanks

Abhik

> -----Original Message-----
> **From:** Duara, Shahnaz [mailto:SDuara@med.miami.edu]
> **Sent:** Wednesday, November 23, 2005 11:36 AM
> **To:** Michele Walsh; Das, Abhik; Higgins, Rose; Finer, Neil; Donovan, Edward (DONOVAEF); Carlo, Wally; Rich, Wade; Newman, Nancy
> **Subject:** RE: RBC Non SUPPORT Saturation Data
>
> Hi Michele et al;
>
> I agree that its going to be really important to weed out the RA+vent, cpap or cannula kids, if possible, because they appropriately add high sats to the mix. We don't use Masimos clinically so I don't have additional clinical data that we could add to the mix.
>
> Shahnaz
>
> > -----Original Message-----
> > **From:** Michele Walsh [mailto:mcw3@case.edu]
> > **Sent:** Wednesday, November 23, 2005 11:18 AM
> > **To:** Das, Abhik; Higgins, Rose; Finer, Neil; Donovan, Edward (DONOVAEF); Carlo, Wally; Duara, Shahnaz; Rich, Wade; Newman, Nancy
> > **Subject:** RBC Non SUPPORT Saturation Data
> >
> > Hi All!
> > As we suspected, the kids outside of the trial have sats even higher- at least at RB&C. We have downloaded the Massimo data on 9 non-SUpport kids enrolled in a desaturation study. These data are collected in an identical manner to the SUPPORT kids and meet all the other entry criteria except they are not randomized to an oxygen intervention. Five were on vents, 3 on cpap, and 1 in nasal cannula. Thus, they are managed under routine

conditions for our nursery which is stated as sat 90-95%.
It is important to note that this DOES include time when they are in room air. We will try to pull out the data for these patients and times- and reanalyze.
However, the SUPPORT data is also subject to that same bias for kids on RA vent, RA cpap, RA nc. Was the DSMC aware of this? Can RTI pull out the sats for these types of interventions?
To summarize the distribution:
> 95% sat - 56% (range 38-86)
90-95% sat - 26% (range 8-33%)
85-89% sat - 8% (range 2-13%)
< 85% sat - 11% (range 3-25%)
I am attachng the file here.
Michele

From: Avroy A. Fanaroff
To: Neil Finer; "Edward Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Michele Walsh
Cc: Das Abhik; Wade Rich; "MD" "Maynard Rasmussen"; "Ken Poole"; "Betty Hastings"; "Michele"; "Wally Carlo"; "Shahnaz Duara"
Subject: Re: re sat distribution data
Date: Wednesday, November 23, 2005 3:56:12 PM

Hi,
happy Thanksgiving all
It is disturbing to enter the Thanksgiving on this sour note of the trial being suspended
I think that Neil is on target with his comments and proposed plan of action
This is at least the 4th time in the history of the Network that a trial has been interrupted or discontinued after an interim analysis. That in of itself is worth reporting. If you add the Kristi Watterberg trail to the mix that makes 5. Given the extraordinary effort to get the design and implementation of the trial correct, how can we avoid these interruptions in the future?
Regards
Avroy

-------*Original Message*-------

From: Michele Walsh
Date: 11/23/05 15:37:43
To: Neil Finer; 'Edward Donovan'; 'Higgins, Rosemary (NIH/NICHD)'; nfiner@ucsd.edu
Cc: Das, Abhik; Wade Rich; 'MD' 'Maynard Rasmussen'; 'Ken Poole'; 'Betty Hastings'; 'Michele'; 'M.D.' 'Avroy A. Fanaroff'; 'Wally Carlo'; 'Shahnaz Duara'
Subject: Re: re sat distribution data

I agree with all of Neils comments! Did the DSMC see if the FiO2 was different which was the intent?
Michele
----- Original Message -----
From: Neil Finer
To: 'Higgins, Rosemary (NIH/NICHD)' ; 'Edward Donovan' ; 'Michele Walsh' ; Neil Finer
Cc: 'Shahnaz Duara' ; 'Wally Carlo' ; 'M.D.' 'Avroy A. Fanaroff' ; 'Michele' ; 'Betty Hastings' ; 'Ken Poole' ; 'MD' 'Maynard Rasmussen' ; Wade Rich
Sent: Wednesday, November 23, 2005 3:30 PM
Subject: RE: re sat distribution data

Hello All

I agree with Ed's comments. In fact we wanted to create different oxygen exposures and the way to do this was to have different periods of time at different SpO2 levels, and it would appear that we have succeeded.

I am also uncertain why non blinded data was evaluated. Our previous comments were that some units were experiencing that the high alarms were not being set. We did not postulate that this was an issue for one or other arm of the trial, but rather a response to frequent alarms. It is the alarms that work to keep the babies in range.

Also we need to understand that the design of the algorithms was also to push the infants into the middle range. I will try to explain this. For an infant whose oximeter displays 88% to 92% when the

actual SpO2 is 91% to 95%, as the true, SpO2 increases toward 95%, the display will increase to 95% to 96% and the alarm can be activated (with the appropriate time delay etc) at actual values of 94-95%. Thus this infant will alarm when the actual SpO2 is BELOW the upper limit of 95%. This will tend to keep the infant more within the desired target range. The same will happen for infants in the lower range, in that when their actual SpO2 is 87%, the display will show 85% and any further decrease will trigger the alarm.

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2. We would additionally hope that an analysis will show excessive time at 96% which actually may represent values from 93% to 96%
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Please consider these suggestions and let me know your thoughts and suggestions

I would like to be prepared for our Monday call.

Have a great Thanksgiving

Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 23, 2005 6:48 AM
To: Edward Donovan; Michele Walsh; Neil Finer
Cc: Shahnaz Duara; Wally Carlo; M.D.' 'Avroy A. Fanaroff; Michele; Betty Hastings; Ken Poole; MD' 'Maynard Rasmussen; Wade Rich
Subject: RE: re sat distribution data

Betty will send it out within the next hour.

Thanks
Rose

and < 85% are different than what is normally experienced for ELBW infants. We need to know the percentage of time at the single value of 96% and probably similarly at 85%. Some values of 96% will actually represent values that should be within the 92% to 95% range, but we will have no ability to know this.
I believe that if we achieve close to 60% within 85% to 95% with the current skews, that we will achieve FiO2 differences.
STOP ROP kept the high range infants at > 95% for > 90% of the time. I am uncertain as to the known risk of any value for SpO2 > 95% below 90%.
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-----Original Message-----
From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Tuesday, November 22, 2005 1:52 PM
To: Laptook, Abbot; Finer, Neil; Higgins, Rose
Subject: re sat distribution data

Hi Rose:
Another thought about sat distribution data. We have Abbot's study at Dallas that looks at distribution of sats as well. Perhaps we can look at this as well.
I will let you know about the Case non Support data.
Michele

From: Tyson, Jon E
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT PI CALL
Date: Wednesday, November 23, 2005 3:47:00 PM

No though I really want to be. (I believe Alice told Carolyn when I would be unavailable- please let me know if there was a mix up).

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

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 23, 2005 1:41 PM
To: Tyson, Jon E
Subject: SUPPORT PI CALL

Jon
Would you be available on Wed. Nov 30 from 9:30-1030 AM EST (8:30-9:30 CST)?
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From:	Petrie, Carolyn
To:	wrich@ucsd.edu; Hastings, Betty J.; Zaterka-Baxter, Kristin; Alice.J.Reardon@uth.tmc.edu; nirupama_laroia@urmc.rochester.edu; Walid.Salhab@UTsouthwestern.edu; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; D"Angio, Carl; Brenda Poindexter; Brenda.H.Morris@uth.tmc.edu; Krisa Van Meurs; Gantz, Marie; Petrie, Carolyn; poo@rti.org; barbara_stoll@oz.ped.emory.edu; Charles.Rosenfeld@UTSouthwestern.edu; dale_phelps@urmc.rochester.edu; Das, Abhik; dstevenson@stanford.edu; edward.donovan@chmcc.org; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; jlemons@iupui.edu; Jobea0@chmcc.org; jon.e.tyson@uth.tmc.edu; alaptook@WIHRI.org; mcw3@cwru.edu; moshea@wfubmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; sduara@miami.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; WOh@wihri.org
Cc:	aellison@med.miami.edu; echaisso@iupui.edu; bvecchio@careNE.org; (b) (6) debra.camputaro@yale.edu; diane.timmer@cchmc.org; fmartinez@ucsd.edu; Karen.Kirby@UTSouthwestern.edu; Ktownsen@med.wayne.edu; KGilley@CareNE.org; lisa.joo@stanford.edu; msumner@peds.uab.edu; mazie_tinsley@oz.ped.emory.edu; renee.dunbar-scott@oz.ped.emory.edu; Jensen, Rosemary; gonza025@mc.duke.edu; Wendy Holcomb
Subject:	SUPPORT call for the NRN, Wed, Nov 30, 9:30-10:30am ET (6:30-7:30am PT)
Date:	Wednesday, November 23, 2005 2:59:11 PM
Importance:	High

The NRN conference call to discuss potential strategies to resume the SUPPORT Trial is scheduled for

Wednesday, November 30th
9:30-10:30am ET (6:30-7:30am PT)

To join the call,

Dial Toll Free, 866-675(b) (6)
Passcode: (b) (6)

PIs: Please ensure that every center is represented for this call.

Carolyn Petrie Huitema
Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 902
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Duara, Shahnaz
To: nfiner@ucsd.edu; Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; Higgins, Rosemary (NIH/NICHD) [E]; Ken Poole; Michele; Shahnaz Duara; Wade Rich; Wally Carlo
Cc: Maynard Rasmussen, MD; Michele Walsh
Subject: RE: re sat distribution data
Date: Wednesday, November 23, 2005 2:12:11 PM

Hi,

The safety issue is hyperoxia, which is not possible even with a sat of 100% in 21% oxygen. With supplemental oxygen, its another story... limiting use of the Masimo (and indirectly the oximeter data collection) to periods of supplemental oxygen is a way to separate the 2 issues, but contamination of dumps with RA data may not be only problem. From what Abhik describes, RTI excluded all known RA days from the analysis, so the only way the data set could get contaminated would be if an 'oxygen' day was a misnomer, allowing inclusion of babies who spent most of the day in RA with a brief period of extra oxygen to be labeled 'oxygen'. Sats may be appropriate during the day to the level of support he/she is getting, but the dumps don't help us sort that out. Not being able to collect continuous FiO2 data simultaneously is the confounder. One way out would be to require significant numbers of hours (? > 12 h) of supplemental oxygen before a day can be labeled an 'oxygen' day - otherwise call it a RA day and forget about analyzing the dump for that day. It sounds arbitrary but so is our current approach.

Couldn't we turn the safety issue around and focus on the 100% sat value, since that is the value where hyperoxia could occur on supplemental oxygen? Spending 36% of the time with sats >95% is concerning only within context.

Happy Thanksgiving to all of you - I'm outta here !

Shahnaz

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 23, 2005 1:18 PM
To: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
Cc: 'Maynard Rasmussen, MD'; 'Michele Walsh'
Subject: FW: re sat distribution data

Hello All
Here is the data for room air only
If SpO2s > 95% are toxic without consideration of the FiO2, then we will need to provide nitrogen to all the NICUs Be well Neil

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, November 23, 2005 7:57 AM
To: nfiner@ucsd.edu; Das, Abhik
Subject: RE: re sat distribution data

Neil,

I've attached a table showing percent of time in each oximeter display range for infants on room air. Room air was defined as FiO2=0.21 or Mode of Support=7 (No Support) on SUPP05 or Oxygen=N or Highest Level of Support=7 (No Support) on SUPP11. Note that, for infants in the LOW oxygenation group, the display range of >95% includes actual SpO2 levels of 93-95%.

Our programmers are working on getting us the data for the actual >95% range broken out into finer units.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone (919) 485-7780
Fax (919) 485-7762
mgantz@rti.org

-----Original Message-----
From: Das, Abhik
Sent: Wednesday, November 23, 2005 8:30 AM
To: 'nfiner@ucsd.edu'; 'Michele Walsh'; 'Higgins, Rosemary (NIH/NICHD)'
Cc: 'Maynard Rasmussen, MD'; 'Avroy A. Fanaroff, M.D.'; Hastings, Betty J.; 'Ed Donovan'; Poole, W. Kenneth; 'Michele'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'; Gantz, Marie; Schaefer, Scott E.
Subject: RE: re sat distribution data

Neil:

We are already working on this (i.e., percentage for each SpO2 value over 95% ie percent at 96%, 97% 98% 99% and 100%). We will also look at the actual percentage of time in the various ranges for all of the infants (non corrected data) for the time only in room air.

Thanks

Abhik

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, November 22, 2005 7:06 PM
To: nfiner@ucsd.edu; 'Michele Walsh'; 'Higgins, Rosemary (NIH/NICHD)'
Cc: 'Maynard Rasmussen, MD'; 'Avroy A. Fanaroff, M.D.'; Hastings, Betty J.; 'Ed Donovan'; Poole, W. Kenneth; 'Michele'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'; Das, Abhik
Subject: RE: re sat distribution data

Hi Again
While we are it, we should ask RTI to look at the percentage for each SpO2 value over 95% ie percent at 96%, 97% 98% 99% and 100%. This will help especially with values at 100%. If there is an issue of the study

creating separate oxygen groups, then the analysis should be looking at the FiO2 exposure to see if we have created different oxygen exposures. I would favor mimimal analyses at this point and trial continuation, with perhaps a change in alarm limits. Let's think about all of this and try to talk on the phone next Monday Be well Neil

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, November 22, 2005 3:31 PM
To: 'Michele Walsh'; 'Higgins, Rosemary (NIH/NICHD)'
Cc: 'Maynard Rasmussen, MD'; 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
Subject: RE: re sat distribution data

Hi Michele and all
I have reviewed Abbot's abstract and he found that the SpO2 was > 95% for about 17% of the time. In addition the skew for correcting the stored values in the oximeter back to real unaltered values is such that for the group in high range ie 88% to 92% is actually 91% to 95%, in the process of correcting, there are a number of real, actual SpO2 values - 93%, 94%, 95% and 96% which are all converted to a display value of 96% because of rounding of decimal points (The Masimo cannot display decimals and we had agreed to this formula as 96% cannot be linked to 4 different actual SpO2 values).
We were aware of this, and used this because we wished to maintain the separation over the widest range. This will represent a problem in reviewing the unskewed data in that there will be an over-representation of values at 96% for the high range infants and 85% for the low range infants.
RTI in converting the data back to "normal" will only see a 96% value for any value of 93%, 94% or 95% or 96% in the 91-95% target infants, and thus we will find a much increased percentage for the actual value of 96% after data conversion, as was done.
We therefore need to look at the value of 96% separately, as we do for 85% We need to understand that values of 96% after conversion will represent actual values of anywhere from 93 to 96%.
However we had agreed that this would not be realistic so that fractions were assigned most of which if corrected to a full integer would read 96%.

This now raises the issue of the study intent and design. We did not design the trial to produce different SpO2s but rather to use the SpO2 to create different oxygen exposures. To my knowledge we did not analyze the FiO2 for the 2 groups. In addition we do not know at present if the % of time > 95% and < 85% are different than what is normally experienced for ELBW infants. We need to know the percentage of time at the single value of 96% and probably similarly at 85%. Some values of 96% will actually represent values that should be within the 92% to 95% range, but we will have no ability to know this. I believe that if we achieve close to 60% within 85% to 95% with the current skews, that we will achieve FiO2 differences.
STOP ROP kept the high range infants at > 95% for > 90% of the time. I am uncertain as to the known risk of any value for SpO2 > 95% below 90%. I also believe that we may increase our time in the narrow and broader ranges by lowering the low alarm to 80% and the high alarm to 94%. Lets think all of this over. Rose, can you ask Marie Ganz to provide us the

actual percentage of time in the various ranges for all of the infants (non corrected data) for the time only in room air. She previously gave us in oxygen and overall. The room air only will provide a ranges of SpO2 > 95% and we can look at this in interpreting the percent time > 96%.

I believe that we can probably move ahead with the trial and I am prepared to argue for this. In spite of this, have a peaceful and restful Thanksgiving Neil

-----Original Message-----
From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Tuesday, November 22, 2005 1:52 PM
To: Laptook, Abbot; Finer, Neil; Higgins, Rose
Subject: re sat distribution data

Hi Rose:
Another thought about sat distribution data. We have Abbot's study at Dallas that looks at distribution of sats as well. Perhaps we can look at this as well. I will let you know about the Case non Support data.
Michele

From: David Stevenson
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Petrie, Carolyn
Subject: Re: FW: SUPPORT conference call
Date: Wednesday, November 23, 2005 1:59:44 PM

Rose,

David could probably do either one. On November 30, he has a meeting already scheduled to start at 7:15am and could be on the conference call for 45 minutes. Does that give you enough time?

December 1 and 2, David is out of the office for (b) (6) . Since the conference call will start very early our time, that may also be a possibility.

I most likely will talk to him later today and could ask him, but you probably want to get this set before then. I would say to go with whatever time works best for everyone else and I will add it to David's calendar.

Thanks,
Lisa

At 10:53 AM 11/23/2005, Higgins, Rosemary (NIH/NICHD) wrote:

> David or Lisa
> Is there any way David could do
> Nov 30 9:30-10:30 (6:30-7:30 PST)
> Or
> Dec 1 10-11 (7-8 PST)
>
> Thanks so much for your help!!
> Rose
>
> ---
>
> **From:** Higgins, Rosemary (NIH/NICHD)
> **Sent:** Wednesday, November 23, 2005 1:52 PM
> **To:** Charles Rosenfeld; 'Richard Ehrenkranz'; 'Barbara Stoll'; alaptook@WIHRI.org
> **Cc:** 'Petrie, Carolyn'
> **Subject:** FW: SUPPORT conference call
> **Importance:** High
>
> HI,
> Can you let Carolyn know potential availability for the following dates for an urgent Steering Committee PI call for SUPPORT ASAP? We would like to set up the call before the end of today!!
>
> Wed Nov 30
> Thurs Dec 1
>
> Thanks
> Rose

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Wednesday, November 23, 2005 9:59 AM
To: poo@rti.org; barbara_stoll@oz.ped.emory.edu; Charles.Rosenfeld@UTSouthwestern.edu; dale_phelps@urmc.rochester.edu; Das, Abhik; dstevenson@stanford.edu; edward.donovan@chmcc.org; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD); jlemons@iupui.edu; Jobea0@chmcc.org; jon.e.tyson@uth.tmc.edu; alaptook@WIHRI.org; mcw3@cwru.edu; moshea@wfubmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; sduara@miami.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; WOh@wihri.org
Cc: Alice.J.Reardon@uth.tmc.edu; aellison@med.miami.edu; echaisso@iupui.edu; (b) (6) ; diane.timmer@cchmc.org; fmartinez@ucsd.edu; Karen.Kirby@UTSouthwestern.edu; debra.camputaro@yale.edu; Ktownsen@med.wayne.edu; KGilley@CareNE.org; lisa.joo@stanford.edu; msumner@peds.uab.edu; mazie_tinsley@oz.ped.emory.edu; renee.dunbar-scott@oz.ped.emory.edu; Jensen, Rosemary; gonza025@mc.duke.edu; Wendy Holcomb; Hastings, Betty J.; Zaterka-Baxter, Kristin; Petrie, Carolyn; Gantz, Marie; wrich@ucsd.edu
Subject: SUPPORT conference call
Importance: High

Please send your availably for this urgent and important conference call regarding the SUPPORT trial.
I will schedule a SUPPORT subcommittee call first (Mon or Tues) and then a second call with the NRN PIs (Wed or Thurs).

If you are unable, please send the availability for the Alt-PI or trial PI at the site.

Mon Nov 28
Tues Nov 29
Wed Dec 1
Thurs Dec 2

Thank you!

Carolyn Petrie Huitema
Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 902
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Michele Walsh
To: Das, Abhik; Duara, Shahnaz; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Donovan, Edward (DONOVAEF); Carlo, Wally; Rich, Wade; Newman, Nancy
Cc: Gantz, Marie; Poole, W. Kenneth
Subject: Re: RBC Non SUPPORT Saturation Data
Date: Wednesday, November 23, 2005 1:15:15 PM

Abhik: The issue is when kids are on RA but still on a vent, or on RA but still on cpapor nc, we are still collecting saturation data but have no ability to lower the sat by weaning FiO2- these would have to be excluded from the data for the DSMC in order for their conclusion to be correct that the babes are at risk from inappropriately high saturation.
Another alternative for the group to consider is to take kids off the sat monitor when in RA regardless of the pressure support- I recognize we have been around this track before- but perhaps we need to reconsider.
REgards, Michele

----- Original Message -----
From: Das, Abhik
To: Duara, Shahnaz ; Michele Walsh ; Higgins, Rose ; Finer, Neil ; Donovan, Edward (DONOVAEF) ; Carlo, Wally ; Rich, Wade ; Newman, Nancy
Cc: Gantz, Marie ; Poole, W. Kenneth
Sent: Wednesday, November 23, 2005 11:57 AM
Subject: RE: RBC Non SUPPORT Saturation Data

The hours reported in the tables that the DSMC saw (and which you have now been sent) are for days on supplemental O2 only; so we have taken out days the infants are on room air (defined as FiO2=0.21 or Mode of Support=7 (No Support) as per SUPP05 or Oxygen=N or Highest Level of Support=7 (No Support) as per SUPP11). However, it is possible that there are times on the supplemental O2 days that the babies are actually on room air; but we have tried to exclude time on room air from the tables that the DSMC saw as best we could.

Thanks

Abhik

-----Original Message-----
From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Wednesday, November 23, 2005 11:36 AM
To: Michele Walsh; Das, Abhik; Higgins, Rose; Finer, Neil; Donovan, Edward (DONOVAEF); Carlo, Wally; Rich, Wade; Newman, Nancy
Subject: RE: RBC Non SUPPORT Saturation Data

Hi Michele et al;

I agree that its going to be really important to weed out the RA+vent, cpap or cannula kids, if possible, because they appropriately add high sats to the mix. We don't use Masimos clinically so I don't have additional clinical data that we could add to the mix.

Shahnaz

-----Original Message-----
From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Wednesday, November 23, 2005 11:18 AM
To: Das, Abhik; Higgins, Rose; Finer, Neil; Donovan, Edward (DONOVAEF); Carlo, Wally; Duara, Shahnaz; Rich, Wade; Newman, Nancy
Subject: RBC Non SUPPORT Saturation Data

Hi All!
As we suspected, the kids outside of the trial have sats even higher- at least at RB&C.
We have downloaded the Massimo data on 9 non-SUpport kids enrolled in a desaturation study. These data are collected in an identical manner to the SUPPORT kids and meet all the other entry criteria except they are not randomized to an oxygen intervention. Five were on vents, 3 on cpap, and 1 in nasal cannula. Thus, they are managed under routine conditions for our nursery which is stated as sat 90-95%.
It is important to note that this DOES include time when they are in room air. We will try to pull out the data for these patients and times- and reanalyze.
However, the SUPPORT data is also subject to that same bias for kids on RA vent, RA cpap, RA nc. Was the DSMC aware of this? Can RTI pull out the sats for these types of interventions?
To summarize the distribution:
> 95% sat - 56% (range 38-86)
90-95% sat - 26% (range 8-33%)
85-89% sat - 8% (range 2-13%)
< 85% sat - 11% (range 3-25%)
I am attachng the file here.
Michele

From: Neil Finer
To: "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Cc: "Maynard Rasmussen, MD"; "Michele Walsh"
Subject: FW: re sat distribution data
Date: Wednesday, November 23, 2005 1:17:47 PM
Attachments: Pct in display range (room air) 11-23-05.rtf

Hello All
Here is the data for room air only
If SpO2s > 95% are toxic without consideration of the FiO2, then we will need to provide nitrogen to all the NICUs
Be well
Neil

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, November 23, 2005 7:57 AM
To: nfiner@ucsd.edu; Das, Abhik
Subject: RE: re sat distribution data

Neil,

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Our programmers are working on getting us the data for the actual >95% range broken out into finer units.

Marie

Marie Gantz, Ph.D.
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Telephone (919) 485-7780
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-----Original Message-----
From: Das, Abhik
Sent: Wednesday, November 23, 2005 8:30 AM
To: 'nfiner@ucsd.edu'; 'Michele Walsh'; 'Higgins, Rosemary (NIH/NICHD)'
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We are already working on this (i.e., percentage for each SpO2 value

over 95% ie percent at 96%, 97% 98% 99% and 100%). We will also look at the actual percentage of time in the various ranges for all of the infants (non corrected data) for the time only in room air.

Thanks

Abhik

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Sent: Tuesday, November 22, 2005 7:06 PM
To: nfiner@ucsd.edu; 'Michele Walsh'; 'Higgins, Rosemary (NIH/NICHD)'
Cc: 'Maynard Rasmussen, MD'; 'Avroy A. Fanaroff, M.D.'; Hastings, Betty J.; 'Ed Donovan'; Poole, W. Kenneth; 'Michele'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'; Das, Abhik
Subject: RE: re sat distribution data

Hi Again
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-----Original Message-----
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Sent: Tuesday, November 22, 2005 1:52 PM
To: Laptook, Abbot; Finer, Neil; Higgins, Rose
Subject: re sat distribution data

Hi Rose:
Another thought about sat distribution data. We have Abbot's study at Dallas that looks at distribution of sats as well. Perhaps we can look at this as well. I will let you know about the Case non Support data.
Michele

PERCENT OF TIME SPENT IN EACH RANGE (OXIMETER DISPLAY)
DAYS ON ROOM AIR*

Center Number	Total number of hours	<85	>=85 and <88	TARGET >=88 and <=92	>92 and <=95	>95
3	5915.3	7.5	2.3	12.1	10.0	68.1
4	2847.0	3.4	1.7	13.0	8.3	73.6
9	726.7	3.4	0.8	7.2	8.5	80.1
11	1959.0	4.4	2.5	17.2	7.9	68.1
12	1081.0	2.5	3.0	24.8	11.1	58.7
13	703.7	3.5	4.1	26.9	7.4	58.0
14	6429.2	3.0	1.4	9.8	7.7	78.1
18	615.4	5.4	1.0	8.8	11.1	73.7
22	4803.9	5.0	2.1	16.1	9.0	67.9
Total	**26607.4**	**4.6**	**1.9**	**13.4**	**8.8**	**71.3**

*Days on room air are defined as FiO2=0.21 or Mode of Support=7 (No Support) on SUPP05 or Oxygen=N or Highest Level of Support=7 (No Support) on SUPP11

**For infants in the LOW oxygenation group, the display range of >95% includes actual SpO2 levels of 93-95%

Centers with <500 total hours are not displayed but are included in total

From: Edward Donovan
To: Michele Walsh; Higgins, Rosemary (NIH/NICHD) [E]; Shahnaz Duara; Wally Carlo; Nancy Newman; Abhik Das; Neil Finer; Wade Rich
Subject: Re: RBC Non SUPPORT Saturation Data
Date: Wednesday, November 23, 2005 12:36:41 PM

---

good points, Michele

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0180
Fax 513-636-0171
www.cincinnatichildrens.org/cprc

>>> "Michele Walsh" <mcw3@case.edu> 11/23/2005 11:18:06 AM >>>
Hi All!
As we suspected, the kids outside of the trial have sats even higher- at least at RB&C.
We have downloaded the Massimo data on 9 non-SUpport kids enrolled in a desaturation study. These data are collected in an identical manner to the SUPPORT kids and meet all the other entry criteria except they are not randomized to an oxygen intervention. Five were on vents, 3 on cpap, and 1 in nasal cannula. Thus, they are managed under routine conditions for our nursery which is stated as sat 90-95%.
It is important to note that this DOES include time when they are in room air. We will try to pull out the data for these patients and times- and reanalyze.
However, the SUPPORT data is also subject to that same bias for kids on RA vent, RA cpap, RA nc. Was the DSMC aware of this? Can RTI pull out the sats for these types of interventions?
To summarize the distribution:
> 95% sat - 56% (range 38-86)
90-95% sat - 26% (range 8-33%)
85-89% sat - 8% (range 2-13%)
< 85% sat - 11% (range 3-25%)
I am attachng the file here.
Michele

From: Avroy A. Fanaroff
To: Neil Finer; Neil Finer; Wally Carlo M.D.
Cc: Michele Walsh; MD" "Maynard Rasmussen; Avroy A. Fanaroff M.D.; Betty Hastings; Ed Donovan; Higgins, Rosemary (NIH/NICHD) [E]; Ken Poole; Michele; Shahnaz Duara; Wade Rich
Subject: RE: re sat distribution data
Date: Wednesday, November 23, 2005 11:31:38 PM

Don't you guys ever take a break
happy holidays
We have been pelted with snow - it has become a Thanksgiving tradition
One that I would readily surrender
Wally, in the real world, which this trial was designed for in the long run, you cannot demand a specialist at the bedside to monitor the saturation monitor.
We need to modify the study to separate the groups
Av

-------Original Message-------

From: Wally Carlo, M.D.
Date: 11/23/05 23:20:06
To: Neil Finer; Neil Finer
Cc: Michele Walsh; MD' 'Maynard Rasmussen; Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; higginsr@mail.nih.gov; Ken Poole; Michele; Shahnaz Duara; Wade Rich
Subject: RE: re sat distribution data

In Poets study, it was a bedside person who achieved the same performance as the servo control. wally

---

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 23, 2005 9:18 PM
To: Wally Carlo, M.D.; Neil Finer
Cc: 'Michele Walsh'; 'MD' 'Maynard Rasmussen'; 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Shahnaz Duara'; 'Wade Rich'
Subject: RE: re sat distribution data

Thanks Wally

Would this be someone at the bedside or a person to assist with reviewing the monitor ranges etc. One concern that I have would be the reproducibility of using such an individual. While a number of studies have shown the value of servo control – most recently Poets study, It is doubtful that a manufacturer will develop such a device in view of the potential liability.

Let's keep thinking about other options

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2005 1:28 PM
To: Neil Finer

Cc: Michele Walsh; MD' 'Maynard Rasmussen; Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; higginsr@mail.nih.gov; Ken Poole; Michele; Neil Finer; Shahnaz Duara; Wade Rich
Subject: RE: re sat distribution data

Neil:

A recent study of pulse oximetry by servocontrol or dedicated person showed extremely high compliance with the saturation targets. I believe it was 80-90%. I think we should consider adding resources to have a dedicated person achieve high compliance.

Wally

From: Neil Finer [mailto:nfiner@pedsmail.ucsd.edu]
Sent: Wednesday, November 23, 2005 2:57 PM
To: Wally Carlo, M.D.
Cc: Michele Walsh; MD' 'Maynard Rasmussen; Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; higginsr@mail.nih.gov; Ken Poole; Michele; Neil Finer; Shahnaz Duara; Wade Rich
Subject: RE: re sat distribution data

Wally

Do you have any suggestions for helping to keep us in the narrower target levels? Another option is a redesign of the oximeters, or a simple shift of 3-5% for all values as in BOOST. This may produce better separation throughout, but is problematic at the high ranges.

With regards to great clinical care, we do not have any data as to the ideal SpO2 ranges that we should target. No such data has ever been collected and this was an aim of this trial. We need the ranges to be tested with the relevant outcomes, but I agree with the DSMC that we also need separation.

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2005 12:48 PM
To: Neil Finer; Higgins, Rosemary (NIH/NICHD); Edward Donovan; Michele Walsh; Neil Finer
Cc: Shahnaz Duara; M.D.' 'Avroy A. Fanaroff; Michele; Betty Hastings; Ken Poole; MD' 'Maynard Rasmussen; Wade Rich
Subject: RE: re sat distribution data

Hi:
I think it is important that everyone is aware of usual sats in NICUs. Michele's data is helpful. The multicenter study I mentioned yesterday is also helpful. Nonetheless, we should strive to provide great clinical care, not just do great trials.

I agree that we want different O2 exposures but we must remember that in part, that differential exposure is best accomplished while the infants are at a saturation 88-92%. I like Neil's idea of lower alarm levels but I suspect, it will reduce but not eliminate the problem.

I think it is important to compare our data with that of other trials such as the BOOST one, which also

show a high frequency of sats >95%.

Wally

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 23, 2005 2:30 PM
To: 'Higgins, Rosemary (NIH/NICHD)'; 'Edward Donovan'; 'Michele Walsh'; Neil Finer
Cc: 'Shahnaz Duara'; Wally Carlo, M.D.; 'M.D.' 'Avroy A. Fanaroff'; 'Michele'; 'Betty Hastings'; 'Ken Poole'; 'MD' 'Maynard Rasmussen'; Wade Rich
Subject: RE: re sat distribution data

Hello All

I agree with Ed's comments. In fact we wanted to create different oxygen exposures and the way to do this was to have different periods of time at different SpO2 levels, and it would appear that we have succeeded.

I am also uncertain why non blinded data was evaluated. Our previous comments were that some units were experiencing that the high alarms were not being set. We did not postulate that this was an issue for one or other arm of the trial, but rather a response to frequent alarms. It is the alarms that work to keep the babies in range.

Also we need to understand that the design of the algorithms was also to push the infants into the middle range. I will try to explain this. For an infant whose oximeter displays 88% to 92% when the actual SpO2 is 91% to 95%, as the true, SpO2 increases toward 95%, the display will increase to 95% to 96% and the alarm can be activated (with the appropriate time delay etc) at actual values of 94-95%. Thus this infant will alarm when the actual SpO2 is BELOW the upper limit of 95%. This will tend to keep the infant more within the desired target range. The same will happen for infants in the lower range, in that when their actual SpO2 is 87%, the display will show 85% and any further decrease will trigger the alarm.

In reviewing the DSMC comments I believe that our strategy moving forward should be as follows:

1. We should strenuously argue that the percent of time over 95% in NOT a safety issue as there is no antecedent data that such SpO2s for such a duration, ie 35% > 95% are toxic. We would argue that this duration is actually lower than may be expected.
2. We would additionally hope that an analysis will show excessive time at 96% which actually may represent values from 93% to 96%
3. I would suggest that we change the low alarm to 80% and the high to 94%. This should push us toward the narrow targets
4. We need to rewrite the manual and protocol to clarify that we are aiming to produce different oxygen exposures using different SpO2 limits
5. I would fight vigorously to continue the trial as is, and re-evaluate the oximetry data after a further 100-200 infants
6. If we are forced to consider dropping the oximetry arm, then have all the Masimo oximeters converted to normal and continue to use them to collect the data about the actual SpO2 exposures of this population which will still be unique and incredibly useful in looking at durations of hyperoxia and hypoxia in the ELBW and their outcomes.

Please consider these suggestions and let me know your thoughts and suggestions

I would like to be prepared for our Monday call.

Have a great Thanksgiving

Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 23, 2005 6:48 AM
To: Edward Donovan; Michele Walsh; Neil Finer
Cc: Shahnaz Duara; Wally Carlo; M.D.' 'Avroy A. Fanaroff; Michele; Betty Hastings; Ken Poole; MD' 'Maynard Rasmussen; Wade Rich
Subject: RE: re sat distribution data

Betty will send it out within the next hour.

Thanks
Rose

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Wednesday, November 23, 2005 9:46 AM
To: 'Michele Walsh'; Higgins, Rosemary (NIH/NICHD); Neil Finer
Cc: 'Shahnaz Duara'; 'Wally Carlo'; M.D.' 'Avroy A. Fanaroff; 'Michele'; 'Betty Hastings'; 'Ken Poole'; MD' 'Maynard Rasmussen; 'Wade Rich'
Subject: RE: re sat distribution data

Do we have any details on this issue?
What I understand is that there is a concern about exposure to high O2 sat disproportionately in one arm? If it's the "high" arm, then this is the purpose of the study, i.e. to see if decreasing oxygen exposure reduces BPD and ROP. Am I missing the boat? When are we going to see the actual concerns of the DSMC?

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0180
Fax 513-636-0171
www.cincinnatichildrens.org/cprc

>>> "Neil Finer" <nfiner@ucsd.edu> 11/22/2005 6:30:43 PM >>>

Hi Michele and all
I have reviewed Abbot's abstract and he found that the SpO2 was > 95% for

about 17% of the time.
In addition the skew for correcting the stored values in the oximeter back to real unaltered values is such that for the group in high range ie 88% to 92% is actually 91% to 95%, in the process of correcting, there are a number of real, actual SpO2 values - 93%, 94%, 95% and 96% which are all converted to a display value of 96% because of rounding of decimal points (The Masimo cannot display decimals and we had agreed to this formula as 96% cannot be linked to 4 different actual SpO2 values).
We were aware of this, and used this because we wished to maintain the separation over the widest range. This will represent a problem in reviewing the unskewed data in that there will be an over-representation of values at 96% for the high range infants and 85% for the low range infants.
RTI in converting the data back to "normal" will only see a 96% value for any value of 93%, 94% or 95% or 96% in the 91-95% target infants, and thus we will find a much increased percentage for the actual value of 96% after data conversion, as was done.
We therefore need to look at the value of 96% separately, as we do for 85%
We need to understand that values of 96% after conversion will represent actual values of anywhere from 93 to 96%.
However we had agreed that this would not be realistic so that fractions were assigned most of which if corrected to a full integer would read 96%.

This now raises the issue of the study intent and design. We did not design the trial to produce different SpO2s but rather to use the SpO2 to create different oxygen exposures. To my knowledge we did not analyze the FiO2 for the 2 groups. In addition we do not know at present if the % of time > 95% and < 85% are different than what is normally experienced for ELBW infants.
We need to know the percentage of time at the single value of 96% and probably similarly at 85%. Some values of 96% will actually represent values that should be within the 92% to 95% range, but we will have no ability to know this.
I believe that if we achieve close to 60% within 85% to 95% with the current skews, that we will achieve FiO2 differences.
STOP ROP kept the high range infants at > 95% for > 90% of the time. I am uncertain as to the known risk of any value for SpO2 > 95% below 90%.
I also believe that we may increase our time in the narrow and broader ranges by lowering the low alarm to 80% and the high alarm to 94%.
Lets think all of this over.
Rose, can you ask Marie Ganz to provide us the actual percentage of time in the various ranges for all of the infants (non corrected data) for the time only in room air. She previously gave us in oxygen and overall. The room air only will provide a ranges of SpO2 > 95% and we can look at this in interpreting the percent time > 96%.

I believe that we can probably move ahead with the trial and I am prepared to argue for this.
In spite of this, have a peaceful and restful Thanksgiving
Neil

-----Original Message-----
From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Tuesday, November 22, 2005 1:52 PM
To: Laptook, Abbot; Finer, Neil; Higgins, Rose
Subject: re sat distribution data

Hi Rose:
Another thought about sat distribution data. We have Abbot's study at

Dallas that looks at distribution of sats as well. Perhaps we can look at this as well.
I will let you know about the Case non Support data.
Michele

From:	Michele Walsh
To:	Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Donovan, Edward (DONOVAEF); Carlo, Wally; Duara, Shahnaz; Rich, Wade; Newman, Nancy
Subject:	RBC Non SUPPORT Saturation Data
Date:	Wednesday, November 23, 2005 11:18:27 AM
Attachments:	percent ranges.xls

Hi All!
As we suspected, the kids outside of the trial have sats even higher- at least at RB&C.
We have downloaded the Massimo data on 9 non-SUpport kids enrolled in a desaturation study. These data are collected in an identical manner to the SUPPORT kids and meet all the other entry criteria except they are not randomized to an oxygen intervention. Five were on vents, 3 on cpap, and 1 in nasal cannula. Thus, they are managed under routine conditions for our nursery which is stated as sat 90-95%.
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Michele

(b) (6)	<85	85-89	90-95	>95	total
	3.1	6.4	32.9	57.7	100.1
	4	4.5	19.3	72.3	100.1
	3.5	2.4	8.3	85.6	99.8
	19.3	12.2	29.2	39.3	100
	25.4	13.1	26.4	35.1	100
	18.52	11.9	30.7	38.9	100.02
	10.2	8.7	29.4	51.7	100
	8.7	7.9	29.2	54.2	100
	4.9	4.2	24.2	66.7	100
mean	10.84667	7.922222	25.51111	55.72222	
sd	8.241578	3.87162	7.592504	16.91292	

From: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Trial
Date: Wednesday, November 23, 2005 10:56:34 AM

---

can you tell what line we are so i can guage the level of problem we have?
ron

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

11/23/2005 10:54 AM

To "Ronald N Goldberg" <goldb008@mc.duke.edu>
cc
Subject RE: SUPPORT Trial

You are center 19, but the data are de-identified in this list.

Rose

From: Ronald N Goldberg [mailto:goldb008@mc.duke.edu]
Sent: Wednesday, November 23, 2005 10:50 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Fw: SUPPORT Trial

Hi Rose,
which center are we?
Ron

----- Forwarded by Ronald N Goldberg/Pediatrics/mc/Duke on 11/23/2005 10:48 AM -----

"Hastings, Betty J." <bkh@rti.org>

11/23/2005 09:55 AM

To <brenda.H.Morris@Uth.tmc.edu>, <cotte010@mc.duke.edu>, <crosen@mednet.swmed.edu>, <vanmeurs@leland.stanford.edu>, <Maynard.Rasmussen@sharp.com>, <alaptook@wihri.org>, <Jobea0@chmcc.org>, <bpoindex@iupui.edu>, <edward.donovan@chmcc.org>, <jlemons@iupui.edu>, <moshea@wfubmc.edu>, <nfiner@ucsd.edu>, <sshankar@med.wayne.edu>, <sduara@miami.edu>, <susie.buchter@oz.ped.emory.edu>, <wcarlo@peds.uab.edu>, <mcw3@cwru.edu>, <Vineet.bhandari@yale.edu>, <vivek.Narendran@cchmc.org>, <Walid.Salhab@UTSouthwestern.edu>, "[SCRN] Stoll, Barbara" <barbara_stoll@oz.ped.emory.edu>, <dale_phelps@urmc.rochester.edu>, <dstevenson@stanford.edu>, <jon.e.tyson@Uth.tmc.edu>, <richard.ehrenkranz@yale.edu>, <goldb008@mc.duke.edu>, <Walid.Salhab@UTSouthwestern.edu>, <ahensman@wihri.org>, <mbball@leland.stanford.edu>, <grisbyca@email.uc.edu>, <ellen_hale@oz.ped.emory.edu>, <gaynelle.hensley@UTSouthwestern.edu>, "Georgia E McDavid" <Georgia.E.McDavid@Uth.tmc.edu>, <auten002@mc.duke.edu>, <linda_reubens@urmc.rochester.edu>, <lucmille@iupui.edu>, <mcollins@peds.uab.edu>, <monica.konstantino@yale.edu>, <Nancy.Miller@UTSouthwestern.edu>, "Nancy Newman" <nxs5@cwru.edu>, <npeters@wfubmc.edu>, <ae5357@wayne.edu>, <risa.demetrio@sharp.com>, <jyhall@stanford.edu>, <kathy.arnell@sharp.com>, <Reverett@med.miami.edu>, <wrich@ucsd.edu>, <rbridge@ucsd.edu>, <Nirupama_Laroia@urmc.rochester.edu>, <srhintz@stanford.edu>, <Maynard.Rasmussen@sharp.com>, <Barbara.Alexander@cchmc.org>, "Lenora Jackson" <Lenora.Jackson@uc.edu>, "Estelle E. Fischer" <estelle.fischer@cchmc.org>, "Holly Mincey" <minceyhl@email.uc.edu>, "Jody Shively" <jody.shively@cchmc.org>, "Kate Bridges, MD"

<Kathleen.Bridges@cchmc.org>

cc "Das, Abhik" <adas@rti.org>, "Poole, W. Kenneth" <poo@rti.org>, "Zaterka-Baxter, Kristin" <kzaterka@rti.org>, <higginsr@mail.nih.gov>

Subject FW: SUPPORT Trial

Dear All,

As you all have been informed by Dr. Higgins, the SUPPORT Trial has been temporarily suspended effective November 22, 2005. Enclosed, as an attachment, is a memo describing the rationale and supporting data for suspending the trial. The SUPPORT Subcommittee plans to meet, by phone, early next week and their recommendations will be sent to the Steering Committee. A Steering Committee call will then be scheduled to discuss these recommendations.

For patients currently enrolled on the study protocol, they can remain on the protocol. Strict adherence to the saturations targets must be emphasized. For infants enrolled in the MRI secondary study, they can have their assessments and if patients have already been enrolled in the SUPPORT primary study, they can be approached for the MRI secondary study.

Thanks.

Betty

<<Pct in each O2 range 11-18-051.doc>> <<DSMCMemotosites 11-22-05 adrev.doc>>

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
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Fax: (919) 485-7762
bkh@rti.org

From: Michele Walsh
To: Edward Donovan; Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer
Cc: "Shahnaz Duara"; "Wally Carlo"; M.D." "Avroy A. Fanaroff; "Michele"; "Betty Hastings"; "Ken Poole"; MD" "Maynard Rasmussen; "Wade Rich"
Subject: Re: re sat distribution data
Date: Wednesday, November 23, 2005 10:52:08 AM

Neil: I think the data of interest are the pre-intervention data that Abbot and Walid collected. In these data, the babes had sat > 94% 24.2% of the time. We are looking at our data that we have collected as part of the desat study in non-SUPPORT patients. Will send that as soon as I have it. Michele

----- Original Message -----
From: Edward Donovan
To: 'Michele Walsh' ; Rosemary (NIH/NICHD)' 'Higgins ; Neil Finer
Cc: 'Shahnaz Duara' ; 'Wally Carlo' ; M.D.' 'Avroy A. Fanaroff ; 'Michele' ; 'Betty Hastings' ; 'Ken Poole' ; MD' 'Maynard Rasmussen ; 'Wade Rich'
Sent: Wednesday, November 23, 2005 9:46 AM
Subject: RE: re sat distribution data

Do we have any details on this issue?
What I understand is that there is a concern about exposure to high O2 sat disproportionately in one arm? If it's the "high" arm, then this is the purpose of the study, i.e. to see if decreasing oxygen exposure reduces BPD and ROP. Am I missing the boat? When are we going to see the actual concerns of the DSMC?

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0180
Fax 513-636-0171
www.cincinnatichildrens.org/cprc

>>> "Neil Finer" <nfiner@ucsd.edu> 11/22/2005 6:30:43 PM >>>
Hi Michele and all
I have reviewed Abbot's abstract and he found that the SpO2 was > 95% for about 17% of the time.
In addition the skew for correcting the stored values in the oximeter back to real unaltered values is such that for the group in high range ie 88% to 92% is actually 91% to 95%, in the process of correcting, there are a number of real, actual SpO2 values - 93%, 94%, 95% and 96% which are all converted to a display value of 96% because of rounding of decimal points (The Masimo cannot display decimals and we had agreed to this formula as 96% cannot be linked to 4 different actual SpO2 values).
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We need to understand that values of 96% after conversion will represent actual values of anywhere from 93 to 96%.
However we had agreed that this would not be realistic so that fractions

From: Das, Abhik
To: nfiner@ucsd.edu; Michele Walsh; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Maynard Rasmussen, MD; Avroy A. Fanaroff, M.D.; Hastings, Betty J.; Ed Donovan; Poole, W. Kenneth; Michele; Shahnaz Duara; Wade Rich; Wally Carlo; Gantz, Marie; Schaefer, Scott E.
Subject: RE: re sat distribution data
Date: Wednesday, November 23, 2005 8:30:14 AM

Neil:

We are already working on this (i.e., percentage for each SpO2 value over 95% ie percent at 96%, 97% 98% 99% and 100%). We will also look at the actual percentage of time in the various ranges for all of the infants (non corrected data) for the time only in room air.

Thanks

Abhik

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, November 22, 2005 7:06 PM
To: nfiner@ucsd.edu; 'Michele Walsh'; 'Higgins, Rosemary (NIH/NICHD)'
Cc: 'Maynard Rasmussen, MD'; 'Avroy A. Fanaroff, M.D.'; Hastings, Betty J.; 'Ed Donovan'; Poole, W. Kenneth; 'Michele'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'; Das, Abhik
Subject: RE: re sat distribution data

Hi Again
While we are it, we should ask RTI to look at the percentage for each SpO2 value over 95% ie percent at 96%, 97% 98% 99% and 100%. This will help especially with values at 100%. If there is an issue of the study creating separate oxygen groups, then the analysis should be looking at the FiO2 exposure to see if we have created different oxygen exposures. I would favor mimimal analyses at this point and trial continuation, with perhaps a change in alarm limits. Let's think about all of this and try to talk on the phone next Monday Be well Neil

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, November 22, 2005 3:31 PM
To: 'Michele Walsh'; 'Higgins, Rosemary (NIH/NICHD)'
Cc: 'Maynard Rasmussen, MD'; 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
Subject: RE: re sat distribution data

Hi Michele and all
I have reviewed Abbot's abstract and he found that the SpO2 was > 95% for about 17% of the time. In addition the skew for correcting the stored values in the oximeter back to real unaltered values is such that for the group in high range ie 88% to 92% is actually 91% to 95%, in the process of correcting, there are a number of real, actual SpO2 values - 93%, 94%, 95% and 96% which are all converted to a display value of 96% because of rounding of decimal points (The Masimo cannot display decimals and we had agreed to this formula as 96% cannot be linked to 4

From:	Wally Carlo, M.D.
To:	nfiner@ucsd.edu; Michele Walsh; Higgins, Rosemary (NIH/NICHD) [E]
Cc:	Maynard Rasmussen, MD; Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; Ken Poole; Michele; Shahnaz Duara; Wade Rich; Das, Abhik
Subject:	RE: re sat distribution data
Date:	Tuesday, November 22, 2005 7:15:20 PM

I just want to make sure we are all aware that many studies looking at sats/PaO2 have shown high sats routinely used in preemies. There was one abstract at PAS of the multicenter study on pulse ox monitoring by Cindy Cole and collaborators showing the high sats maintained in the US. We were the center with the lowest sats and our average was 92% even though we aim for 90%. In one of the initial benchmarking pilot data collection, I think similar findings were observed on day 1 (with PaO2s, Michele: Correct my terrible memory). However, it will be good to be aware of the problem and try to address is. wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, November 22, 2005 6:06 PM
To: nfiner@ucsd.edu; 'Michele Walsh'; 'Higgins, Rosemary (NIH/NICHD)'
Cc: 'Maynard Rasmussen, MD'; 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; 'Ken Poole'; 'Michele'; 'Shahnaz Duara'; 'Wade Rich'; Wally Carlo, M.D.; 'Das, Abhik'
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Sent: Tuesday, November 22, 2005 3:31 PM
To: 'Michele Walsh'; 'Higgins, Rosemary (NIH/NICHD)'
Cc: 'Maynard Rasmussen, MD'; 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
Subject: RE: re sat distribution data

Hi Michele and all
I have reviewed Abbot's abstract and he found that the SpO2 was > 95% for about 17% of the time.
In addition the skew for correcting the stored values in the oximeter back to real unaltered values is such that for the group in high range ie 88% to 92% is actually 91% to 95%, in the process of correcting, there are a number of real, actual SpO2 values - 93%, 94%, 95% and 96% which are all converted to a display value of 96% because of rounding of decimal points (The Masimo cannot display decimals and we had agreed to

this formula as 96% cannot be linked to 4 different actual SpO2 values).

We were aware of this, and used this because we wished to maintain the separation over the widest range. This will represent a problem in reviewing the unskewed data in that there will be an over-representation of values at 96% for the high range infants and 85% for the low range infants.
RTI in converting the data back to "normal" will only see a 96% value for any value of 93%, 94% or 95% or 96% in the 91-95% target infants, and thus we will find a much increased percentage for the actual value of 96% after data conversion, as was done.
We therefore need to look at the value of 96% separately, as we do for 85% We need to understand that values of 96% after conversion will represent actual values of anywhere from 93 to 96%.
However we had agreed that this would not be realistic so that fractions were assigned most of which if corrected to a full integer would read 96%.

This now raises the issue of the study intent and design. We did not design the trial to produce different SpO2s but rather to use the SpO2 to create different oxygen exposures. To my knowledge we did not analyze the FiO2 for the 2 groups. In addition we do not know at present if the % of time > 95% and < 85% are different than what is normally experienced for ELBW infants.
We need to know the percentage of time at the single value of 96% and probably similarly at 85%. Some values of 96% will actually represent values that should be within the 92% to 95% range, but we will have no ability to know this.
I believe that if we achieve close to 60% within 85% to 95% with the current skews, that we will achieve FiO2 differences.
STOP ROP kept the high range infants at > 95% for > 90% of the time. I am uncertain as to the known risk of any value for SpO2 > 95% below 90%.
I also believe that we may increase our time in the narrow and broader ranges by lowering the low alarm to 80% and the high alarm to 94%.
Lets think all of this over.
Rose, can you ask Marie Ganz to provide us the actual percentage of time in the various ranges for all of the infants (non corrected data) for the time only in room air. She previously gave us in oxygen and overall.
The room air only will provide a ranges of SpO2 > 95% and we can look at this in interpreting the percent time > 96%.

I believe that we can probably move ahead with the trial and I am prepared to argue for this.
In spite of this, have a peaceful and restful Thanksgiving Neil

-----Original Message-----
From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Tuesday, November 22, 2005 1:52 PM
To: Laptook, Abbot; Finer, Neil; Higgins, Rose
Subject: re sat distribution data

Hi Rose:
Another thought about sat distribution data. We have Abbot's study at Dallas that looks at distribution of sats as well. Perhaps we can look

at this as well.
I will let you know about the Case non Support data.
Michele

From: Michele Walsh
To: Laptook, Abbot; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: re sat distribution data
Date: Tuesday, November 22, 2005 4:52:33 PM

Hi Rose:
Another thought about sat distribution data. We have Abbot's study at Dallas that looks at distribution of sats as well. Perhaps we can look at this as well.
I will let you know about the Case non Support data.
Michele

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: support
Date: Tuesday, November 22, 2005 4:32:20 PM

Do you mean, I need to get a hold of Noah because of the huge flood?

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 22, 2005 4:31 PM
To: Petrie, Carolyn
Subject: RE: support

Noah

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Tuesday, November 22, 2005 4:30 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: support

Do you need help tracking folks down?

Carolyn Petrie Huitema
Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 902
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Kathy J Auten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ronald N Goldberg; cotte010@mc.duke.edu
Subject: Re: SUPPORT
Date: Tuesday, November 22, 2005 3:25:31 PM

Duke is fine. Have a good holiday.
Kathy

Kathy J. Auten, BA, MSHS
Neonatal Research Coordinator
Duke University Medical Center
Box 3179
Durham, NC 27710 USA
919-681-5859 tel
919-681-4868 fax
kathy.auten@duke.edu

"Higgins, Rosemary \(NIH/NICHD\)" <higginsr@mail.nih.gov> wrote on 11/22/2005 11:26:11 AM:

> Hi everyone,
> Since Thanksgiving may be a four day holiday at many institutions,
> please assess your SUPPORT oximeters TODAY. If you think you may
> need additional oximeters over the long holiday weekend, let me know
> ASAP so that we insure time for shipping.
>
> Happy Thanksgiving to Everyone!!!
> Rose
>
> Rosemary D. Higgins, M.D.
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine
> NICHD, NIH
> 6100 Executive Blvd., Room 4B03B
> MSC 7510
> Bethesda, MD 20892
> (For overnight delivery, use Rockville, MD 20852)
> 301-435-7909
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov
>

From: Das, Abhik
To: Hastings, Betty J.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Tuesday, November 22, 2005 2:48:56 PM
Attachments: Pct in each range (supp O2) 11-18-052 rev.doc

Rose:

If you email this to the PIs, you can also include the table that the DSMC saw (attached), minus the center indicators.

Thanks

Abhik

<<Pct in each range (supp O2) 11-18-052 rev.doc>>

-----Original Message-----
From: Hastings, Betty J.
Sent: Tuesday, November 22, 2005 2:36 PM
To: higginsr@mail.nih.gov
Cc: Das, Abhik
Subject: SUPPORT

Rose,
Dr. Avery just had one minor change. He suggested changing "this" data to "these" data. Do you want me to resend this to you?

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

PERCENT OF TIME SPENT IN EACH O2 RANGE
(INCLUDES DAYS ON SUPPLEMENTAL O2 ONLY)

LOW TREATMENT GROUP

Center Number	Total number of hours	<85	Low target 85-89	90	High target 91-95	>95	Mean O2 level
	12140.8	24.2	16.3	4.5	42.4	12.7	88.9
	1271.4	8.6	16.0	4.6	45.5	25.3	92.4
	828.2	11.1	13.0	4.2	49.0	22.7	92.0
	1678.3	18.2	16.2	4.7	47.5	13.3	90.0
	4446.4	13.5	11.6	3.5	51.8	19.4	91.5
	3234.6	19.9	25.1	4.6	37.5	12.8	89.0
	10495.5	17.8	16.9	4.7	44.9	15.6	90.4
	1.8	12.5	5.4	1.7	70.0	10.4	91.6
	2281.5	21.0	18.8	5.3	42.2	12.6	89.0
	2505.3	20.1	20.6	5.7	44.2	9.5	89.6
	267.5	14.8	18.3	5.8	50.5	10.4	90.7
	1910.2	15.0	16.3	5.1	49.7	13.9	90.6
	518.0	25.0	16.2	4.3	39.7	14.8	89.0
	5090.1	16.4	16.2	4.7	45.9	16.9	90.7
Total	**46669.7**	**18.9**	**16.9**	**4.6**	**44.7**	**14.9**	**90.0**

HIGH TREATMENT GROUP

Center Number	Total number of hours	<85	Low target 85-89	90	High target 91-95	>95	Mean O2 level
	7256.8	12.0	10.3	2.6	29.8	45.2	92.0
	888.2	3.2	6.0	1.9	31.6	57.3	95.0
	705.6	3.1	9.4	3.1	47.6	36.8	93.5
	3306.3	10.7	14.1	3.9	44.4	26.8	91.2
	7441.0	9.1	12.1	3.1	37.9	38.0	92.3
	6545.0	8.9	12.0	3.5	38.5	37.0	92.3
	641.5	2.6	6.4	2.3	32.7	56.1	94.6
	7236.3	6.5	15.0	4.3	45.5	28.8	92.1
	6449.2	9.3	14.1	4.0	46.3	26.4	91.4
	1448.7	13.5	13.9	3.2	30.9	38.5	91.3
	474.9	5.8	12.2	3.9	51.1	27.2	92.3
	325.5	5.2	13.1	4.1	47.3	30.6	92.6
	444.3	10.9	15.6	5.1	52.2	16.2	90.2
	14865.1	7.0	11.4	3.3	39.0	39.2	92.7
Total	**58028.3**	**8.6**	**12.3**	**3.4**	**39.5**	**36.2**	**92.2**

Data last updated 11/7/2005. Includes 153 infants.

From:	Roy Heyne
To:	Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; newman@rti.org; petrie@rti.org; jon.e.tyson@uth.tmc.edu; moshea@wfubmc.edu; bvohr@wihri.org
Subject:	Fwd: Motor Function NF05 --Some Issues Not Yet Resolved
Date:	Monday, November 21, 2005 1:55:59 PM

I sent this on the 12th but am not sure if any of you got it, since I received no feedback. Hate to beat a dead horse, but doesn't appear that any of these issues are addressed or resolved in the final version of the manual Carolyn just sent out.

Furthermore, in going back over case 3 from our interrator session, it appears we labeled a case of "suspect" increased tone in ankles only, combined with "toe walking", as "mild diplegia". Even if we accept the gait as functional but not fluent, there was not a "definite" tone abnormality. Though our overall definition of CP requires definite tone abnormality, it may be worth reiterating this in the descriptions for the specific types of spastic CP in question 9c. Secondly, if the amount of toe walking displayed by this patient, which I think we debated about in the interrator session, is going to be sufficient to label the child either as mild diplegia (when definite tone abnormality is also present) or as "CP otherwise unclassified" (if tone normal), then I think we need a clearer definition of what constitutes toe walking. Just as brief periods up on toes do not constitute an abnormal positive support reaction (in fact, one must remain up on toes for 30 secs), I'm not sure that brief/intermittent periods up on toes when walking are sufficient to indicate non-fluent gait, never mind CP--especially when the child intermittently comes down off toes and even shows ability to intermittently without rising up on toes. In any case, the instruction for question 9b2 (Hypertonia) indicates that toe walking with normal angles should be coded as "9 Other neurological abnormality in Section B"; if this is intended to refer to the revised 9c10 "Cerebral Palsy Otherwise Unclassified" then the reference needs to be corrected; but as I indicated in #5 below, I still think it is debatable whether toe walking without definite tone abnormality meets our two criteria definition of CP; and think, if it can truly be considered "isolated" abnormal toe walking, then it would be better classified as 9b3--other abnormal (non-CP).

>>> Roy Heyne 11/12/05 4:01 PM >>>
As we were going over the developmental cases on the DVD from our interrator session, several questions arose concerning the revised wording we had discussed during our last conference call.

1) Upper Extremity Tone: Betty's case (#5) was assessed to have suspect decreased tone; but in looking back at our revised operations manual definition on 10-11, we do not address decreased tone at all, either definite or suspect.

2) Lower limb function gait: Dee's case (#1) was assessed to have no independent walking (choice 4 on question 6c), but if in fact the child was able to cruise, or walk with examiner assistance ("hands held") for balance only, we wondered whether she should be rated at level 3, instead, since the previous definition of moderate CP on 10-20 of the manual indicated that "assistive devices include walkers, AFOs, hand(s) held, ... cruising". I don't recall addressing that issue in our last conference call, but I think this case illustrates the need to do so.

3) Speaking of GMF, my staff also raised some questions regarding the correspondence between Lowe limb function gait (LLFG) levels and GMF levels. It seems fairly apparent that LLFG code 1 corresponds to GMF 1 and LLFG 2 to GMF Possible 1. But LLFG 3 could map to either GMF 1 or 2, depending on how we define "device" in the LLFG scheme, and how broadly we interpret "holding on to furniture" in the Palisano wording, and specifically whether we extend the latter so that it covers the same range of assisted modes as "device" in our former definition of moderate CP. This will also determine whether GMF 1 maps to Mild CP, as the current draft has it, or to Moderate CP, if the latter extends down to include children who can cruise, etc. but cannot walk without some "device" assistance.

4) One of our group (not me for a change) wondered why there are two apparent paths to Level 2 on NF05a? They asked why the decision box "Sits hands free for play" doesn't also include all three items in the box to its right, since a child really has to be able to perform all 4 items to qualify for Level 1. Inability to do any of the 4 motor tasks pushes one down the decision tree to Level 2 or greater.

5) In our discussion of our new two-criteria definition of CP, several of the staff questioned how a toe-walker with

normal angles meets both criteria, specifically how (s)he fulfills the abnormality of classical neuro exam element. They thought it was circular/redundant to consider dysfluent gait both a functional disorder and a neuro abnormality. In any case, they thought it would be more appropriate to classify this as other abnormal under the non-CP classification set rather than as other CP.

6) Speaking of the latter, I could not tell from my notes what we finally decided to include under revised #9. Were we going to restrict this to "mixed" CP in the sense of some combination of types 1-8, for example double hemiplegia or asymmetric quad, or just to a combination of spastic CP and dyskinetic CP. And where were we going to put the dyspraxia and maladroit: under 10 (not otherwise classifiable), or, perhaps better yet, under non-CP other? And where did we decide to put facial palsy and vocal cord paralysis?

From:	Newman, Jamie
To:	Stevens, Timothy; Higgins, Rosemary (NIH/NICHD) [E]; Betty Vohr; maegan.c.currence@uth.tmc.edu; SEguaras@med.miami.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; Janet.Morgan@childrens.com; VPhillips@peds.uab.edu; mgfuller@ucsd.edu; lnoel@wihri.org; ldrichar@iupui.edu; lohme001@mc.duke.edu; bjacksn@wfubmc.edu; diane_hust@urmc.rochester.edu; mbball@leland.stanford.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; ellen_hale@oz.ped.emory.edu; dkennedy@dmc.org; Jackie.Hickman@Childrens.com; bss5@cwru.edu; joanne.williams@yale.edu; Nancy; Rebecca Bara; auten002@mc.duke.edu
Cc:	Hastings, Betty J.; Petrie, Carolyn; Das, Abhik; richard.ehrenkranz@yale.edu; jon.e.tyson@uth.tmc.edu; MPeralta@PEDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; apappas@med.wayne.edu; sshankar@med.wayne.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; rdillard@wfubmc.edu; gary_myers@urmc.rochester.edu; bvohr@wihri.org; adusick@iupui.edu; steichjj@email.uc.edu; drfjcmd@aol.com
Subject:	Coordinator Availability for Breathing Outcomes Interview Training
Date:	Thursday, November 17, 2005 5:11:30 PM
Attachments:	SUPPORT BO Protocol 11-17.doc

Dear Follow-up Coordinators,
Attached is the Breathing Outcomes Protocol in case anyone needs it for IRB submission. The Forms and Manual will be distributed in the next few days with the changes discussed during today's call. Please let me know your availability for each of the times below for training to conduct the Breathing Outcomes questionnaires:

Tuesday December 6 from 2-4pm
Wednesday December 7 from 2-4pm
Friday December 9 from 2-4pm
Monday December 13 from 2-4pm

We will most likely have two separate trainings so that everyone will be able to participate. Please let me know if you have any questions.

Thanks, Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

NICHD SUPPORT Trial
Breathing Outcomes Study

University of Rochester
Golisano Children's Hospital at Strong

Timothy P. Stevens, MD, MPH
Peter Szilagyi, MD, MPH
Dale Phelps, MD

Proposal Updated: November 17, 2005

Contact Information:

Timothy P. Stevens, MD
Assistant Professor of Pediatrics
Division of Neonatology
Golisano Children's Hospital at Strong
University of Rochester
601 Elmwood Avenue, Box 651
Rochester, NY 14642
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TABLE OF CONTENTS

Study Protocol

ABSTRACT

Statement of Problem Premature infants have a greater risk of recurrent wheezing and chronic cough and greater need for pulmonary care in early childhood than term infants (1-11). Although Chronic Lung Disease (CLD) is a risk factor, the etiology of symptomatic airway dysfunction, defined hereafter as recurrent wheezing and/or chronic cough, in formerly premature infants is not known.

Hypotheses The goal of this clinical project is to understand better the antecedents of symptomatic airway dysfunction among preterm infants during early childhood by evaluating the effect of treatment with different levels of targeted oxygen saturation in the immediate neonatal period. **The overarching hypothesis is that premature infants exposed to supplemental oxygen suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction and respiratory symptoms when challenged with subsequent environmental or infectious exposures.**

Hypothesis #1- Relative to infants managed with a higher SpO2 range, infants who are managed with a lower targeted SpO2 range will have less symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' corrected age (CA), whether they develop CLD or not.

Hypothesis #2- Relative to infants managed with prophylactic surfactant and conventional ventilation, infants who are managed with the early use of CPAP and a permissive ventilator strategy will have less symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' CA, whether they develop CLD or not.

Design

This study is a longitudinal follow-up of infants enrolled in the SUPPORT Trial to determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care in the first 18-22 months' CA.

Definition of outcomes:

A) Parental Report Symptomatic Airway Dysfunction Defined as Recurrent Wheezing or Chronic Cough
B) Parental Report of Physician Diagnosed Wheezing
C) Volume of Outpatient Pulmonary Care including number of pulmonary medications, office and emergency room visits and re-hospitalizations for respiratory illnesses.

Ascertainment of outcomes:

Outcomes will be measured at 4 time points in the first 18-22 months' CA as follows:

1. NICU discharge -baseline interview at to obtain family and environmental history
2. Six months' CA - telephone or face to face interview to ascertain incidence of symptomatic airway dysfunction and obtain interval history of need for pulmonary care.
3. Twelve months' CA - telephone or face to face interview as at 6 months'
4. 18-22 months' CA- Prior to or as part of the NICHD follow-up clinic visit, a telephone or face to face interview will be conducted to ascertain incidence of symptomatic airway dysfunction and obtain history of need for pulmonary care.

Anticipated Results

We anticipate that, for infants who develop CLD and those who do not, treatment with a lower vs. higher targeted oxygen saturation range will have less symptomatic airway dysfunction and less need for outpatient pulmonary care in the first 18-22 months' CA. We also anticipate that greater use of CPAP compared with conventional management will be associated with less symptomatic airway dysfunction.

Benefits and Risks

The proposed SUPPORT Breathing Outcomes Study will directly measure symptomatic airway dysfunction and outpatient pulmonary morbidity in infants treated with either a higher vs. lower targeted oxygen saturation. These data will provide important insight into the effect of different levels of supplemental oxygen exposure on airway growth and development in formerly premature infants. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the neurodevelopmental follow up visit. We anticipate no risk to patients enrolled in this observational follow-up study.

B. STATEMENT OF THE PROBLEM

Premature infants have a greater risk for recurrent wheezing, chronic cough and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor, the etiology of symptomatic airway dysfunction, defined hereafter as recurrent wheezing and/or chronic cough, in formerly premature infants is not known.

C. HYPOTHESES

The overarching hypothesis is that premature infants exposed to supplemental oxygen and, to a lesser extent, mechanical ventilation, in the immediate neonatal period suffer oxidant stress in the lung that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction, respiratory symptoms and need for pulmonary care when challenged with subsequent environmental or infectious exposures.

Specific Hypotheses:

Hypothesis #1- We hypothesize that relative to infants managed with a higher SpO2 range, infants managed with a lower SpO2 range will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care at 18-22 months' CA.

Hypothesis #2- We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

Hypothesis #3- We hypothesize that **among infants with CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

Hypothesis #4- We hypothesize that **among infants without CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

D. SPECIFIC AIMS

The goal of this project is to understand better the etiology of symptomatic airway dysfunction among formerly premature infants during early childhood by examining the interaction of oxygen exposure (targeted SpO2 range), surfactant therapy and early nasal CPAP in the newborn period.

SA#1 - Measure the effect of lower vs. higher targeted SpO2 on the incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care among infants born $24^{0/7}$ - $27^{6/7}$ weeks' gestation during the first 18-22 months' CA.

SA#2 - Measure the effect of early CPAP and permissive ventilator strategy compared with prophylactic surfactant and traditional ventilator strategy on the incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care among infants born 24-27 weeks' gestation during the first 18-22 months' CA.

SA#3 – Among infants who develop CLD, determine whether CLD is milder in infants managed with low compared with high targeted SpO2 by measuring incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

SA#4 – Among infants who do not develop CLD, determine whether pulmonary outcome is better for infants managed with a low compared with high targeted SpO2 range by measuring incidence of symptomatic airway dysfunction and need for outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

E. RATIONALE/JUSTIFICATION

Although synergy in producing airway injury may exist between oxygen toxicity and mechanical forces applied to the lung, animal and human data suggest that exposure to high concentrations of supplemental oxygen alone is sufficient to cause airway narrowing and greater airway dysfunction when exposed to subsequent environmental or infectious challenges. Understanding the relative contributions of oxygen toxicity and mechanical forces on airway growth and development may facilitate development of targeted therapies for preventing or reducing symptomatic airway dysfunction in premature infants.

Why measure symptomatic airway dysfunction and outpatient pulmonary care as an outcome from a clinical NICU interventional trial?

1) Important information will be available on the effect of oxidant gas exposure on airway development and later symptomatic airway dysfunction. Exposure to oxidant gas has been causally linked with later wheezing. Existing data on the relationship between supplemental oxygen therapy and wheezing come from longitudinal cohort studies, a design that suffers from intrinsic limitations that make controlling for potential confounders of respiratory outcome difficult. By randomizing infants to higher vs. lower target saturation ranges, and thereby presumably higher or lower concentrations of inspired oxygen, *the SUPPORT Trial creates a unique, and perhaps the only, opportunity to evaluate the effect of different levels of supplemental oxygen on subsequent symptomatic airway dysfunction and need for outpatient pulmonary care after NICU discharge.*
2) Using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care can be directly quantified, allowing assessment of whether infants both with and without CLD have improved pulmonary health as a result of the study intervention.
3) The incidence of CLD, defined as an oxygen requirement at 36 weeks' PMA, is an incomplete measure of pulmonary outcome in formerly premature infants during early infancy. CLD as defined above reflects alveolar gas diffusion and NICU oxygen needs. However, outpatient pulmonary morbidity for formerly premature infants is often airway related, involving wheezing either as a primary symptom such as bronchiolitis or as a complicating symptom of lower respiratory tract infection such as pneumonia. The studies proposed here will directly measure the effect of a randomized NICU-based clinical intervention on symptomatic airway dysfunction and outpatient pulmonary morbidity.
4) The risk of a negative trial is reduced. Because the diagnosis of CLD does not completely predict need for outpatient pulmonary care, clinically significant improvements in pulmonary morbidity may occur with minimal or no change in the incidence of CLD. This result has occurred in other interventional trials in which no difference in CLD were observed (12).
5) At present, there is no standard way to measure symptomatic airway dysfunction in premature infants in NICHD pulmonary intervention trials. There is need for a better measure to assess clinical pulmonary outcome to recognize and promote therapies that reduce need for outpatient care of former extremely premature infants.

F. BACKGROUND / PREVIOUS STUDIES

Recurrent Wheezing In Preterm Infants is a Significant Public Health Problem

Outpatient pulmonary morbidity, especially recurrent wheezing and need for outpatient pulmonary care, is an understudied but clinically important outcome measure for former premature infants with and without CLD. Infants born weighing < 1500 grams (very low birth weight, VLBW) and especially infants born weighing < 1000 grams are at increased risk for small airway narrowing, airway hyperreactivity, wheezing, and nighttime cough (1-11). Up to 30-40% of formerly extremely premature infants have episodes of wheezing after NICU discharge

with many requiring bronchodilators and frequent health care visits. Up to 40-50% of premature infants require re-hospitalization, mostly for treatment of respiratory illnesses (9;12;13). In analysis of cross sectional data from the National Maternal Infant Health Survey and 1991 Longitudinal Follow up Survey, the prevalence of asthma-like recurrent wheezing varied markedly with birth weight. Infants with normal birth weight (NBW, > 2500 grams) had a 6.7% prevalence of asthma compared to 10.9% of low birth weight infants (LBW, 1500-2499 grams) and 21.9% for VLBW (14). Mean per capita asthma related costs have been estimated to be 5 times greater for VLBW compared with NBW infants. The net effect is that VLBW infants, who comprise 2% of asthma patients, consume up to 7% of asthma-related therapy costs (14).

Animal Studies

Animal studies suggest that exposure of the premature lung to hyperoxia (without concomitant mechanical ventilation) for relatively brief periods is sufficient to cause airway remodeling and smooth muscle changes that predispose toward airway narrowing and hyperreactivity to subsequent environmental challenges (15-18). In a rhesus monkey model of asthma, Schlegle et al. exposed infant monkeys to repeated cycles of inhaled House Dust Mite Allergen (HDMA), ozone or filtered air. While repeated exposure to either ozone or HDMA had mild effects, exposure to cycles of ozone followed by HDMA resulted in asthma like changes with significant increases in serum IgE, serum histamine, peripheral eosinophilia and greater airway reactivity. Using supplemental oxygen rather than the stronger oxidant ozone, Schulman et al. found that exposure of newborn guinea pigs to 70% oxygen for 96 hours resulted in airway hyperreactivity at 2 and 9 days after the cessation of oxygen. In cell models, intracellular glutathione buffers airway cells against oxidant injury during hyperoxia (19;20). Although the critical period for lung development is comparatively brief in laboratory animals compared with human infants, the duration of hyperoxic exposure (and risk of oxygen toxicity) for treatment of neonatal lung disease may extend for much longer periods in premature infants known to be deficient in anti-oxidant systems such as intracellular glutathione.

Premature Infants <u>With CLD</u> Are At Greatest Risk For Airway Dysfunction

Among premature infants, infants with bronchopulmonary dysplasia (BPD) are at highest risk for poor pulmonary outcome after NICU discharge. Infants with CLD have small airway compromise with decreased forced expiratory flow velocities, airway hyperreactivity, and increased functional residual volume suggesting airway obstruction (2;5;9;21-24). In a pulmonary follow up of infants with RDS or BPD, De Klein et al. found infants with BPD had reduced FEV1 at baseline while infants with RDS but not BPD had significant improvements in FEV1 following bronchodilator therapy. In this study, a history of recurrent wheezing predicted abnormal pulmonary function (25). In a recent study of infants with CLD, Robin et al. found that 50% of infants with CLD had symptoms of recurrent wheezing and 35% showed significant airway responsiveness to bronchodilators, evidenced by a 24% increase in forced expiratory flow velocity at 75% of expired forced vital capacity (FEF_{75}). This study demonstrated the relationship between recurrent wheezing as a clinical symptom and the physiologic measurement of airway obstruction. Infants with CLD and a history of recurrent wheezing showed greater hyperinflation, expiratory flow limitation and airway responsiveness to albuterol compared to those without a history of recurrent wheezing (24).

Premature Infants <u>Without CLD</u> Have Significant Airway Dysfunction

Among VLBW infants who do not develop CLD, several studies of pulmonary outcome have found an association between neonatal oxygen exposure and increased prevalence of expiratory flow dysfunction and airway hyperreactivity (4;11;26-29). Some authors attribute reductions in airway function to intrinsically small airways as a consequence of poor intrauterine growth rather than superimposed airway injury or reactivity from neonatal respiratory disease (1;30). However, because small airways alone do not fully explain airway hyperreactivity, other mechanisms of small airway dysfunction are necessary to explain respiratory symptoms.

Several pulmonary outcome studies have reported significant increases (2-fold or more) in airway obstruction among VLBW infants without CLD following exposure to as little as 40% oxygen for 5 days (3;4;8;26). Not all studies have had similar results suggesting variability in effect or susceptibility of babies to oxygen exposure (31;32). In 1982, Coates et al. described increased small airway resistance at 10 year follow up of mildly

premature infants (mean gestational age 31 weeks and birth weight 2000 grams) treated with a high oxygen regimen and those exposed to a low oxygen regimen for the treatment of respiratory distress syndrome (RDS). Mechanical ventilation was not used in either group. Pulmonary function tests were performed on survivors receiving either the low or high supplemental oxygen regimen ten years after their initial illness. Infants treated with high levels of supplemental oxygen alone (no mechanical ventilation) had decrements in airway function similar to decrements in function reported for a historical cohort of RDS survivors treated with ventilation and high levels of supplemental oxygen. From these data, the authors concluded that neonatal exposure to high oxygen concentrations in the absence of mechanical ventilation is capable of causing long-term change in small airways (28). These studies suggest that use of lower supplemental oxygen concentration may improve respiratory health of infants who do not develop CLD.

Premature Infants Without CLD Have Increased Risk of Symptomatic Airway Dysfunction and Need for Outpatient Pulmonary Care.

For VLBW infants without CLD, the prevalence of parental or physician reported wheezing is increased compared with term infants, with estimates of the prevalence of wheezing ranging from 10-38% (4;8). Prevalence of wheezing requiring medications is greater compared with term infants. VLBW infants have a 2-4-fold increase in respiratory related re-hospitalization rates compared with term infants (4;8;33-35). Although most studies have found the risk of recurrent wheezing remains elevated throughout childhood, an Australian longitudinal follow-up cohort of VLBW infants found the prevalence of wheezing remained elevated for 2 years then returned to baseline (32;36).

Prevalence of Symptomatic Airway Dysfunction in Formerly Preterm Infants During the Surfactant Era Remains High

With the advent of surfactant therapy, survival of small infants increased dramatically and the incidence of CLD changed minimally (37-40). Classic BPD evolved into the "new CLD" characterized by reduced alveolarization and more variable airway changes (41). Pulmonary follow up studies during the surfactant era showed reduced pulmonary morbidity in surfactant treated patients. Typical of these studies, Sell et al. found the incidence of asthma was significantly lower in infants given synthetic surfactant compared with those given air placebo. Pelkonen et al. performed PFT measurements on 40 children aged 7-12 years who were born before 30 weeks of gestation with an immature surfactant system, and were randomized to one of three treatment groups: prophylactic surfactant, rescue surfactant and placebo (air). Spirometric parameters of children born preterm were compared with those of 20 children born at term. Bronchial obstruction was found in 53% of the prophylactically treated group, in 36% of the rescue group, in 67% of the placebo group, and in 0% of the control group (42). A recent report suggests that the introduction of surfactant therapy markedly altered the pulmonary outcome of premature infants. Published in 2001, the Newborn Lung Project Group reported results of a prospective 12-year follow-up of VLBW infants following the introduction of surfactant therapy (5;8;43). Among infants with CLD, wheezing symptoms decreased from 50 to 16% from the period before compared with the period after surfactant therapy became available. However, among infants without CLD the prevalence of wheezing increased from 14% to 38% with the introduction of surfactant. These data suggest that surfactant therapy has an effect on outpatient respiratory health and underscores the need to consider outpatient pulmonary outcomes in evaluating therapeutic strategies that potentially decrease surfactant replacement therapy.

CLD is an Incomplete Predictor of Outpatient Pulmonary Morbidity

Several authors have looked to respiratory symptoms and need for outpatient pulmonary care as outcome measures for neonatal lung disease (9;10;12;24). In 1988, from a retrospective chart review of 605 premature infants < 1500 grams, Shennan et al. found that the presence of BPD (oxygen requirement at 36 weeks PMA) had a 63% positive predictive value and a 90% negative predictive value for abnormal pulmonary outcome in the first 2 years of age. However, this study from before the era of exogenous surfactant therapy defined abnormal pulmonary outcome as death, oxygen requirement at 40 weeks PMA, 2 or more respiratory related hospital admissions, wheezing requiring drug therapy or persistent wheezing resulting in growth failure, handicap or hypotonia at 1 year of age. Such restrictive criteria for abnormal pulmonary outcome are likely to underestimate the burden of recurrent wheezing on former premature infants and their families. Several recent

interventional studies show that CLD is an incomplete predictor of clinical wheezing and need for outpatient pulmonary care and suggest that differences in oxygen exposure or oxidant stress may affect pulmonary outcome without affecting the incidence of CLD.

Interventional Trials That Did Not Reduce CLD But Did Reduce Outpatient Pulmonary Morbidity.

Recent data in preterm infants treated with human recombinant superoxide dismutase (SOD) found that anti-oxidant therapy did not reduce the incidence of CLD. However, among infants < 27 weeks gestation, SOD therapy resulted in significant reductions in the first year after NICU discharge in the number of emergency room visits and number of re-hospitalizations for respiratory problems and reductions in the need for bronchodilators suggesting a reduced prevalence of wheezing in patients treated with SOD (12). In a randomized, multi-center trial from Helsinki, N acetyl cysteine did not reduce the incidence of CLD. Outpatient pulmonary outcome of these patients has not been reported.

Treatment of Premature Infants With Higher Targeted Oxygen Saturations Is Associated with Poorer Pulmonary Outcome

In the STOP-ROP Study, infants exposed to higher levels of oxygen to achieve a targeted saturation of 96-99% compared with 89-94% had greater risk of adverse pulmonary events including pneumonia, chronic lung disease exacerbations and need for diuretics, oxygen and hospitalization at 3 months' corrected age. *Although all infants in this study had CLD at enrollment, different targeted oxygen saturations were associated with large differences in pulmonary morbidity.* Adverse pulmonary outcomes occurred with differences in FIO2 of as little as 10% for patients treated with ventilation, CPAP or hood (36% $\pm$ 14% vs. 46% $\pm$ 20%, respectively for low vs. high saturation range) and 5% for infants treated with nasal cannula, (26% $\pm$ 6% vs. 31% $\pm$ 11%, respectively for low vs. high saturation range) (44). In a similar study, The Benefits of Oxygen Saturation Targeting (BOOST) Trial randomized infants < 30 weeks' gestation to higher (95-98%) or lower (91-94%) saturations ranges beginning at 32 weeks' PMA to determine whether infants managed with higher targeted saturation range showed better growth and neurodevelopment. As in the STOP-ROP study, need for oxygen therapy was prolonged. Trends towards an increased risk of pulmonary death and fewer outpatient office visits (median 27.5 vs. 31.3, $p < .11$) were seen in the lower targeted oxygen saturation group (13).

Factors In Addition To Prematurity and Oxygen Contribute To Symptomatic Airway Dysfunction

Multiple factors in addition to prematurity and oxygen contribute to the development of airway dysfunction in children (Table 1). In the SUPPORT TRIAL Breathing Outcomes Study, these potential covariates will be measured and controlled for using a randomized trial design. These covariates will also be evaluated as independent predictors of pulmonary outcome in multivariate analyses.

Table 1. ***Important Covariates in Etiology of Recurrent Wheezing***

Demographcis – race, sex, ethnicity, parental factors (educational level, poverty status, and age), and family history of wheezing or atopy.

Environmental – daycare, siblings, crowding, tobacco smoke or wood smoke in the home, pets

Health Services – health care and respiratory medication use appropriate for level of respiratory symptoms

Medical- congenital anatomic airway abnormalities, neonatal sepsis, RSV and other viral infections

G. METHOD/ PROCEDURES

NICHD SUPPORT Trial Breathing Outcomes Study

G.1 Description of study design

This study will add an 18-22 month longitudinal, prospective follow-up study of surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial.

G.2 Definition of study population

Infants with gestational age of $24^{0/7}$-$27^{6/7}$ weeks' gestation by best obstetrical estimate.

Inclusion criteria:

- Enrollment in the SUPPORT Trial
- Survival to hospital discharge
- Consent for enrollment into the Breathing Outcomes Study, obtained either at the time of enrollment into the SUPPORT Trial or separately.

Exclusion criteria

- Refusal of informed consent

G.3 Description of study intervention

Before delivery, infants will be randomized to subsequent management with high vs. low target oxygen saturation according to the SUPPORT Protocol. The SUPPORT Breathing Outcomes Study begins just prior to NICU discharge (Figure 1).

Figure 1.

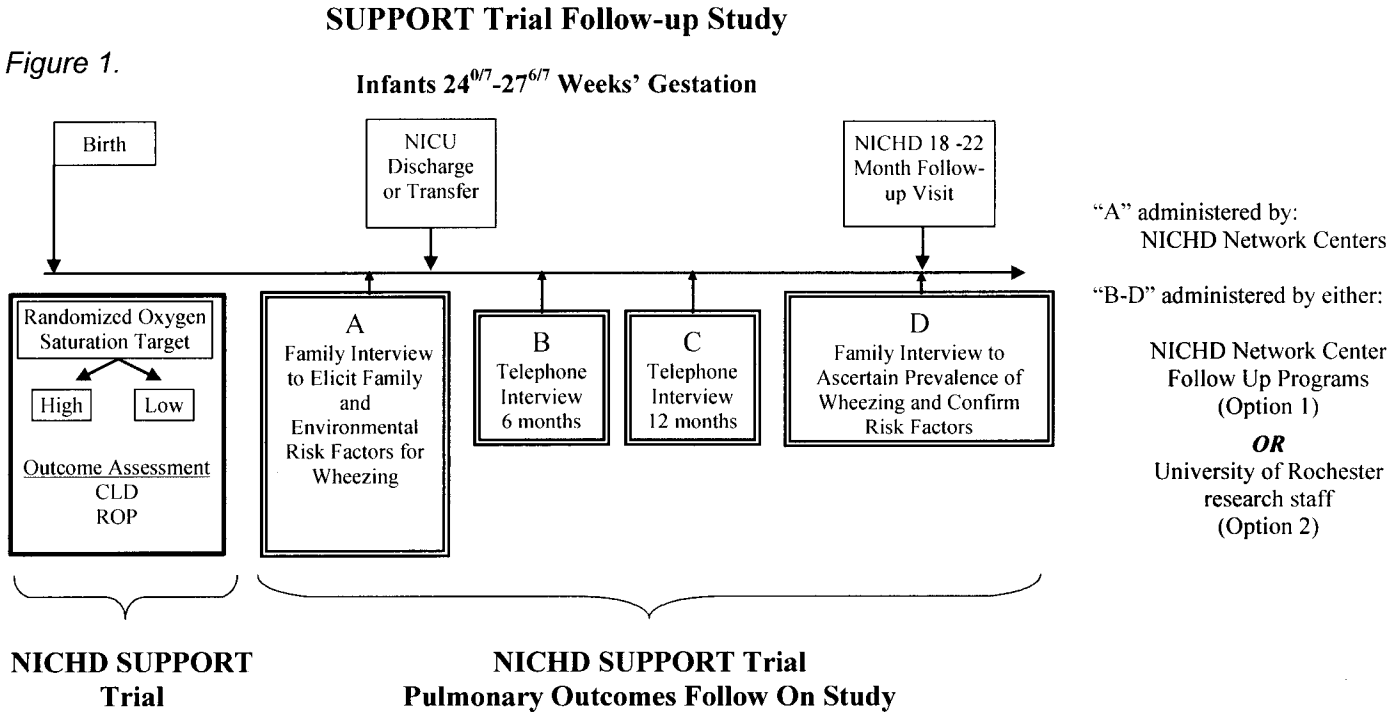

Fig 1, A. Parent (Guardian) Interview to Elicit Family and Environmental Risk Factors for Wheezing and Cough The family interview will be administered either face to face or by telephone to study

participants by site study staff prior to or within 30 days of NICU discharge. The questions are based on intake questions used by the Tucson Respiratory Study and are designed to elicit family history of asthma, atopy, and home environmental exposures and to identify likely care givers (NICU Discharge – Baseline Interview).

Fig 1, B. *Interview at 6 months PMA* – respiratory interval history

Fig 1, C. *Interview at 12 months PMA* – respiratory interval history

Interviews will be undertaken at 6 and 12 months to obtain an interval history of respiratory problems including wheezing, cough, medications used, and health services sought for respiratory related problems (6 and 12 Month Questionnaire). Interviews may be administered either by telephone or face to face.

Fig 1, D. *Parental Interview to Ascertain Incidence of Wheezing and Cough and Confirm Risk Factors*

This parent interview may also be administered either by telephone prior to the regularly scheduled 18-22 month NICHD developmental follow up clinic visit or face to face at the time of the visit. Contacting parents prior to the office visit will help improve the Developmental Follow Up Clinic attendance rate and will allow the clinic visit to provide a back up means to contact the family. The 6, 12 and 18-22 month interviews will be conducted either by the local NICHD Follow Up Program (Option 1) or long distance from Rochester (Option 2), based on center preference (see table 2 below). The interview questionnaires are based on questionnaires administered by the Tucson Respiratory Study at approximately one year of age (18-22 Month Questionnaire). Questions are designed to ascertain the frequency and severity of wheezing and cough episodes and to assess need for outpatient pulmonary care. In addition, risk factors obtained at the 1st interview will be confirmed.

Each interview will collect a 6 month interval history, which, when taken together, will provide a complete respiratory history over the first 18-22 months' corrected age. If one questionnaire is not completed, the subsequent questionnaire will include the full interval history since the last completed questionnaire.

To standardize administration of the interview, the Rochester site will lead an interviewer training program consisting of two parts. Part 1 will consist of a teleconference to discuss study questions and interview script in question by question detail. Part 2 will consist of a practice interview in which interviewers from each center interview the Rochester trainer, who simulates a standardized patient. Following the practice interview, the Rochester trainer and practice interviewer will discuss the interview and give feedback. All interviewers will be required to complete this training.

Table 2. **SUPPORT Trial - Breathing Outcomes Study**

NICHD Site	*6, 12 and 18-22 Month Pulmonary Questionnaires Administered By*	Option Number
Alabama	Alabama	1
Brown	Brown	1
Cincinnati	Cincinnati	1
CWRU	CWRU	1
Dallas	Dallas	1
Duke	Duke	1
Emory	Rochester	2
Houston	Rochester	2
Indiana	Rochester	2
Miami	Miami	1
Rochester	Rochester	2
Stanford	Rochester	2
UCSD	UCSD	1
Wake Forest	Wake Forest	1
Wayne State	Wayne State	1
Yale	Yale	1

G.4 Precise definition of co primary/secondary outcomes

G.4.1 Definition of primary outcomes- parental report of recurrent wheezing and chronic cough.

Two primary outcomes will be measured, the incidence of recurrent wheezing and incidence of chronic cough. Whether individual symptoms (recurrent wheezing or chronic cough, alone) or a combination of these symptoms (wheezing and/or chronic cough, together) best quantifies symptomatic airway dysfunction following premature birth is controversial. Many studies have used wheezing alone as a primary outcome measuring pulmonary morbidity in formerly premature infants (10;12;14;48). In 1996, Greenough, using a combined outcome of either wheezing or chronic cough as a measure of symptomatic airway dysfunction, found that greater pulmonary symptoms were associated with longer durations of supplemental oxygen and mechanical ventilation (49;50). Later, in a follow-up study of infants enrolled in The United Kingdom Oscillator Study (UKOS), Greenough found that frequent wheezing episodes but not chronic cough were associated with neonatal respiratory events (51;52). In our study, to address this issue most conservatively, recurrent wheezing and chronic cough will be measured as co-primary outcomes. Secondary analyses will consider these outcomes in combination.

The incidence of wheezing will be ascertained using the primary question used and validated in the Tucson Children's Respiratory Study (a large prospective birth cohort study of term infants) (53-59), "Has his/her chest ever sounded wheezy or whistling?" (53). Likewise, the incidence of cough will be ascertained using the Tucson question, "Has this child ever had a cough when he/she did not have a cold?" (53). As in Greenough's study, recurrent wheezing will be defined as episodes of wheezing occurring more than twice/week. Chronic cough will be defined similarly, cough occurring as more than twice/week. Additional questions will further characterize the wheezing and coughing episodes, including whether symptoms were associated with a viral illness (parental report of a "cold") or an environmental exposure. A symptom diary will be offered to study participants to help facilitate recall of pulmonary symptoms and need for outpatient pulmonary care.

The Tucson Children's Respiratory Study administered the questionnaires both in person and by phone, depending on patient availability. The investigators did not undertake a formal validation of phone vs. face-to-face administration of the questionnaire. Anecdotally, based on phone conversation with the study coordinator, investigators did not observe a difference in quality of responses between phone and questionnaires administered in person.

G.4.1.1 Standard Definition of Wheezing

Several studies have found that multiple colloquialisms in both English and Spanish can be used to describe wheezing (60-64), creating opportunity for misinterpretation of respiratory sounds and potential for over or under estimation of the incidence of wheezing. Other studies have found that clips of respiratory sounds played for families improve accuracy of symptom reporting (65;66), providing data relatively free from biases due to language, culture, literacy or interviewing techniques. To minimize misinterpretation of other respiratory sounds as wheezing, we will provide a verbal AND a brief audio clip that can be played for the interviewee at the beginning of the interview (electronic clip included separately). Accompanying the audio clip, wheezing will be defined verbally by the interviewer as an expiratory sound (a sound that is made when breathing out, not in) coming from the chest, sometimes described as whistling or musical. Although not yet widely used, use of audio clips to standard symptom definition is the best approach to bridge the language gap that exists between English and Spanish and among Spanish speaking populations using different dialects or colloquialisms.

In administering the questionnaires, every effort will be made to accurately measure the occurrence of pulmonary symptoms and health care and medication use, thus establishing the true incidence of pulmonary morbidity in the study population as a whole. Most importantly, however, because pulmonary morbidity is a blinded outcome of a randomized controlled trial, bias favoring one study arm over another should not occur.

G.4.1.2 Parental Report for Non-English Speaking Populations

Upon finalization of the questionnaires, Spanish language versions will be created and made available to all centers. The Cornell Translation Service, a University based professional translation service, will be contracted to perform the translation. For centers choosing to administer the questionnaires locally (Option 1), each center will be free to choose their primary interviewer who has the necessary skills. Administration of the questionnaire by a native speaker of the local Spanish dialect is recommended. For centers choosing Rochester to administer the questionnaire to their patients (Option 2), English and Spanish speaking individuals, trained to administer the questionnaires, will conduct the telephone or face to face interviews. An audio clip and verbal definition of wheezing will be presented to the respondent to standardize interpretation of wheezing and to minimize ascertainment biases due to language, culture, literacy or interviewing techniques.

G.4.1.3 Parental Report of Pulmonary Symptoms Is a Reliable Outcome Measure of Airway Dysfunction

Evaluation of frequency and severity of respiratory symptoms by parental questionnaire and need for pulmonary care has been used as the primary outcome in multiple follow up studies of term and premature infants (10;12;14;48). A recent review evaluated the value of respiratory symptom history ascertained by parental questionnaire in determining the risk for developing asthma in early childhood. By evaluating 9 large, longitudinal, full term birth cohort studies and reviewing the original questionnaire from 7 of these studies, Koopman found that the questions posed to parents eliciting a history of wheezing in their infants were similar. Parental report of wheezing predicted an increased risk for later respiratory symptoms, including asthma. In the studies proposed here, incidence of recurrent wheezing and chronic cough ascertained by parental report will be primary outcomes, rather than physiologic measurements of airway dysfunction, for several reasons.

G.4.1.4 Reasons to Use Parental Report of Recurrent Wheezing and Chronic Cough as Primary Outcomes

- Parental interview can be performed more readily on large numbers of patients. The validity of this approach has been shown in several longitudinal studies including The Tucson Respiratory Study.
- Recurrent wheezing is highly correlated with changes on pulmonary function testing (PFT). In infants with CLD, a history of wheezing was associated with greater expiratory flow limitation, hyperinflation and airway responsiveness to albuterol on PFT compared to those without such a history (24).
- Parental recall of respiratory illnesses has been shown to correlate strongly with review of medical office records. For asthma and bronchitis in the past year, Pless et al. found good agreement between recall of 288 parents and physician office chart review. Parental education and occupation were not predictive of a parent's ability to recall the illness (67). In an assessment of parental recall done to evaluate minor injury in children, Harel found recall declined with time, with the best recall occurring in the first 3 months after injury with further decline after 6 months from the time of the injury (47;68;69).
- Symptomatic airway dysfunction can be assessed in a standardized way. The NHLBI Consensus Expert Report developed standardized questions to assess severity of airway dysfunction. Three standardized questions from this report will be administered at 6, 12 and 18 months to assess symptom severity (70).

G.4.2 Definition Of Secondary Outcomes - Physician Diagnosed Wheezing. A secondary outcome will be parental report of physician diagnosed wheezing, defined as an episode of wheezing occurring at a health care visit. Physician diagnosed wheezing will be collected by parental report during the telephone or face to face interviews, using the question "Has your child been diagnosed with wheezing by a doctor?"

G.4.3 Definitions of Secondary Outcomes - Measures Need and Volume of Outpatient Pulmonary Care
Important secondary outcomes of outpatient pulmonary morbidity will be collected (Table 3).

Table 3. *Secondary Outcomes, Covariates and Sources*	
Outcomes	**Source**
Secondary Outcomes	
Number and duration of outpatient pulmonary medications including bronchodilator, diuretic, methylxanthine, and inhaled and systemic steroid therapy.	Family interview
Number of office visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview
Number of emergency room visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview
Number of re-hospitalizations for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview
Growth at 18 months PMA (height, weight and head circumference)	NICHD follow up clinic data

G.4.4 Data Collection

Data collection for The Breathing Outcomes Study will be accomplished using one of two options (Figure 2, Table 2). Regardless of Option chosen, each local center will be responsible for obtaining informed consent and tracking patients following discharge.

Consent: For both options, every effort will be taken to enroll ALL SUPPORT patients into the Breathing Outcomes Study, including currently enrolled SUPPORT patients (both patients still in NICU and those discharged) and future enrollees. By obtaining pulmonary outcome data for both current and future SUPPORT patients, death or adverse pulmonary outcome can be analyzed as competing outcomes. Sample consent forms for currently enrolled and future SUPPORT patients are attached.

Figure 2.	Option 1	Option 2	
	Local Center	Local Center	Rochester
Consent / IRB	✓	✓	
Questionnaire at Discharge	✓	✓	
Patient Tracking	✓	✓	
Questionnaire at 6 & 12 mo.	✓		✓
Questionnaire at 18-22 mo.	✓		✓
Data Entry (questionnaires)	✓		✓

G.4.4.1 Data Collection: Ascertainment of Outcomes - Field Work

A. Ascertainment of Wheezing and Outpatient Pulmonary Morbidity By Interview.

There will be 4 parental interviews over 18-22 months, one face to face interview or telephone prior to or within 30 days of NICU discharge and 3 subsequent interviews (by telephone or face to face) at 6 month intervals to collect data on recurrent wheezing, chronic cough and volume of outpatient pulmonary care (Figure 1, A-D above). Based on review of longitudinal studies of full term infants in which follow up patient contacts occurred quarterly to once every 18 months', a 6 month interval for follow up patient contacts is planned in an effort to reduce parental recall omissions which are more likely to occur with less frequent follow up (48;68). The 4 interviews are designed to collect the primary and secondary outcomes of the follow-up study. Other inpatient and outpatient data will be collected as part of the NICHD Neonatal Network Generic Database (GDB) and Follow-up Program.

B. Interview Instruments – Questionnaires are based on the Tucson Children's Respiratory Study, a longitudinal cohort study that followed healthy term infants from birth to over 20 years of age. Questionnaires have been updated with validated symptom severity and tobacco smoke exposure questions, a current list of available respiratory medications and modifications that address health issues faced by formerly premature infants such as use of palivizumab for RSV prophylaxis. The original Tucson questionnaires are designed to elicit a thorough history of possible covariates, such as environmental and infectious exposures and family histories of atopy, asthma or respiratory disease.

C. Administration of Interview Instruments – Six, 12 and 18-22 month interviews will be initiated in one of two ways (table 2):

C.1 Option 1 - NICHD Network Center Follow Up Programs (local contact)

Individual NICHD Network Centers may choose to undertake administration and tracking of patients enrolled in the SUPPORT Breathing Outcomes Study. Local administration of the questionnaires capitalizes on existing NICHD resources available at local centers. Each Network Center choosing local administration of the telephone or face to face questionnaire will identify one or more interviewers who will undergo training in the administration of the questionnaire and tracking of enrolled patients. The Rochester Health Service Research Group will provide training and server as a resource to answer questions regarding administration of the questionnaire (outlined above).

Advantages of Conducting Telephone Interviews From the Local Network Centers

Conducting the telephone interviews from Local Centers will:

1) reduce risk for HIPPA violation
2) capitalize on existing rapport between the patient's family and their local center
3) avoid redundancy in making tracking calls to families

C.2 Option 2 - University of Rochester research staff (long distance contact)

The University of Rochester Neonatology Research Group has conducted similar telephone interview designs as part of an ophthalmologic outcome study of patients enrolled in a randomized trial of cryotherapy to treat ROP and a 15-year, longitudinal neurological assessment conducted by telephone survey among 132 infants treated with surfactant. Telephone follow up rates were 96% follow up at 7 years and 95% follow up at 15 years (71). In the study proposed here, the University of Rochester Health Services Research Group (HSR Group), will conduct the telephone interviews.

In telephone follow up surveys conducted by the HSR Group, follow up rates at 12 months' have exceed 75% in populations at high risk for being lost to follow up (72-78). Working with NICHD Network Centers to assist in tracking local families, follow up rates for this Follow-up Study are expected to exceed 80% and should approach the average annual NICHD follow up rate of 83%.

To facilitate tracking and record keeping, Network Centers choosing Rochester to administer questionnaires to their patients (table 2) will provide contract information to the Rochester site. RTI International will provide monthly updates of patients due for interviews. Local centers will be responsible to maintain updated contact information. Each interview will close with a question as to whether the family plans a new address or phone number prior to the next interview. The names and phone number of a friend or relative will be sought so that they may be contacted in the event that contact with the patient is lost. If contact information is updated, the new contact information will be transmitted back to the local center. By interviewing families every 6 months, a higher follow up rate will be achieved because family contact information will not become so out of date that the family is lost or that re-contacting them is inefficient. We anticipate that each interview will require 2 hours of staff time, with 20-30 minutes to conduct the interview and 90 minutes to contact family and enter data.

Advantages of Conducting Telephone Interviews From a Central Research Facility

Conducting the telephone interviews from Rochester will:

1) require less effort from the individual Network Centers
2) allow standardization of the telephone interview by a core group of trained interviewers
3) blind the telephone interviewer to the SUPPORT Trial study group designation
4) reduce the cost of the study by consolidating the telephone training and follow up at one site.

G.4.4.2 Data Collection: Ascertainment of Environmental and Genetic Covariates

Ascertainment of important environmental exposures and genetic risk factors that might confound the relationship between supplemental oxygen exposure and symptomatic airway dysfunction will be obtained along with the primary outcomes during the same interviews (Table 4). Tobacco smoke exposure is a potentially significant risk factor for airway dysfunction. The tobacco smoke question in the Tucson Study has been replaced by a question shown by Dr. Wakefield et al to correlate with cotinine levels in infants (79;80).

Table 4. Postnatal and Genetic Covariates Evaluated as Potential Confounders of Oxygen and Wheezing

Covariates in Home Environment and Exposures The initial questionnaire and 6 month interviews will gather information on other *inhaled exposures* (tobacco, wood stoves, cold air), *residence* (crowding, siblings, daycare), *infectious exposures* (RSV, palivizumab) and medical risk factors (congenital anatomic airway abnormalities)

Covariates in Family History Questionnaires will elicit *family history* of atopy (family history of asthma, eczema or allergy to foods, pets).

G.4.4.3 Data Collection: Ascertainment of Primary Exposure

Oxygen Exposure

In the SUPPORT Trial, it is assumed that managing infants with a higher vs. lower targeted oxygen saturation range will result in different levels of supplemental oxygen exposure. The SUPPORT Trial will collect data on FIO2 exposure to quantify the anticipated difference. As part of the SUPPORT Trial, FIO2 values will be recorded and analyzed at many time points including time of admission, first blood gas, and as described in the SUPPORT Manual of Operations, Chapter 10 Safety Monitoring Form. Because oxygen is the primary exposure in the SUPPORT Breathing Oucomes Study and plays a central role in the disease model proposed, oxygen exposure will be quantified as described in the main SUPPORT trial and analyzed as a predictor of later symptomatic airway dysfunction.

G.5 Sample size estimate with some statistical support based upon primary outcome

G.5.1 Sample Size

The SUPPORT Trial anticipates enrollment of 1310 patients $\geq 24^{0/7}$ and $\leq 27^{6/7}$ weeks' gestation, providing 80% power to detect a 10% difference between treatment groups in the incidence of death/CLD and death/stage III Retinopathy of Prematurity (ROP). Assuming mortality of 22% for infants in this GA range (NICHD 2001-2002 data), 1021 infants would be expected to survive and be eligible for the SUPPORT Breathing Outcomes study.

Power for detecting a difference between the high vs. low saturation groups for the primary outcome

First we consider power for detecting a difference between the high and low saturation groups for the first primary outcome, recurrent wheezing. We expect the incidence of wheezing to be about 0.17 in the low saturation group and about 0.31 in the high saturation group (12). For the power calculations, we also consider a scenario with a smaller difference between groups: 0.19 for the low saturation group and 0.29 for the high saturation group. We expect the follow up rate to be about 80% (NICHD historical average follow up rate), which would result in data on about 816 patients. We also consider a lower follow up rate of 65%, which would result in about 663 patients. Power to detect a difference between groups based on a chi-square test with type I error alpha set at 0.05 is given in Table 5 for each scenario. From those results, we expect to have more than 80% power for the primary outcome. Also of interest are subgroup analyses, where we look separately at the CLD and non-CLD subjects. Of survivors, we expect 37% or 378 infants to have CLD. For the CLD group, we expect the incidence of wheezing to be about 0.5 in the high saturation group and 0.3 in the low saturation group. If there is a 80% follow up rate, we will have 95% power to detect a difference between the two groups. For the non-CLD subgroup, we expect the incidence to be 0.2 and 0.1 in the high and low groups, respectively. With 80% follow up, we will have 92% power. Thus, we expect to have adequate power for the primary outcome even in the analyses stratified by CLD.

Table 5. Power for primary outcome.

Follow-up rate	Low Saturation	High Saturation	power
80%	0.17	0.31	0.99
80%	0.19	0.29	0.90
65%	0.17	0.31	0.98
65%	0.19	0.29	0.83

Power for detecting a difference between the high vs. low saturation groups for secondary outcomes

We expect the study to be adequately powered for analysis of important secondary outcomes such as use of pulmonary medications. Based on results reported in Davis et al. for infants less than 27 weeks' gestational age [22], we expect the rate of pulmonary medication use to be 0.42 in the high saturation group and 0.19 in the lower saturation group. In that case, even with a 65% follow up rate, we would have more than 99% power to detect a difference between the groups with a chi-square test. Similarly, the CLD subgroup analyses would have more than 80% power under those assumptions. Based on the power numbers above, we could potentially enroll fewer subjects in the trial and still have adequate power. However, we choose to over enroll slightly to make up for the fact that some patients will likely be lost to follow up. The recruitment time will be that of the SUPPORT Trial (2 years) with a run out period of 18-22 months to ascertain follow-up outcomes. The total study period is 36-40 months.

G.5.2 Data Analysis

Analysis of primary dichotomous outcomes will be performed by chi square test and presented as a relative risk for development of that outcome. Number of outpatient pulmonary visits for respiratory illnesses will be presented as median values. The Wilcoxon Rank Sum test, a non-parametric alternative to the two-sample t-test, will be used to test for differences between the two groups. Statistical analyses will need to consider the effect of multiple comparison groups on the level of statistical significance. All analyses will be performed in conjunction with the Research Triangle Institute (RTI, North Carolina). Data will be presented as shown in tables 6-7. Mean FIO2 values in the high and low SpO2 groups will be compared by two sample t-test. Analyses will be done to evaluate the effect of ventilator strategy on pulmonary outcome and presented similarly to table 6 and 7. Other secondary analyses will be performed, including analyses of respiratory outcomes by presence or absence of CLD (oxygen at 36 weeks' PMA determined by SUPPORT study criteria). The incidence of outpatient respiratory diagnoses, such as asthma or reactive airway disease, will be compared between intervention groups and, in sub group analyses, between intervention groups by presence or absence of CLD.

Table 6. *Primary Dichotomous Outcomes*	**Low Saturation**	**High Saturation**	**RR**	**CI**	**p-value**
Parental Report of Recurrent Wheezing (%)					
Parental Report of Chronic Cough (%)					
Need for Outpatient Pulmonary Medications (%)					
Need for Physician Visit for Respiratory Illness (%)					
Need for Re-hospitalization for Respiratory Illness (%)					

Table 7. *Primary Outcomes – Continuous Outcomes*	**Low Saturation**	**High Saturation**	**p-value**
Number of Physician Visit for Respiratory Illness (Median)			
Number of Emergency Visits for Respiratory Illness (Median)			
Number of Re-hospitalization for Respiratory Illness (Median)			

G.5.2 Expected Results

We predict that premature infants managed with a lower targeted oxygen saturation range compared to those managed with a higher targeted oxygen saturation are exposed to lower levels of supplemental oxygen and have reduced risk of recurrent wheezing in the first 18-22 months' CA.

G.5.2 Anticipated Problems and Solutions

1) Participant attrition. As seen in the sample size calculation, the potential for patients to be lost to follow up over time will be offset by over enrolling patients to participate in the follow up. Because patients who enroll in the SUPPORT Trial are randomized, there should be no systematic bias favoring one group over another among patients who are lost to follow up. However, if loss to follow up is in part caused by the treatment or outcomes, this could bias the results. We will therefore investigate whether there are differences in key variables for subjects who are lost to follow up compared to those who remain in the study. For example, we will test whether subjects in one treatment arm were more likely to be lost to follow up than in the other arm. Similarly, we will compare wheezing rates at 6 months' for those who are later lost to follow up compared to those who remain in the study. We do not expect to see any major differences.

2) Difficulty tracking families. With mobile families, keeping contact information up to date may be difficult. To promote successful follow up in both the Breathing Outcome Study described here and the routine NICHD neurodevelopmental follow up visit at 18 - 22 months, each center will be responsible to track families to maintain current contact information for both the family and primary care physician.

3) Center variability in administering the questionnaire. With 11 centers administering the questionnaires, variation in techniques and styles in administering the questionnaires has the potential to introduce ascertainment bias. To minimize this risk, staff administering the questionnaires will undergo an interviewer training program conducted by the Rochester Site. The program will consist of a conference call and a practice interview of a standardized patient.

4) The SUPPORT Breathing Outcomes Study has been prepared as the central project for Dr. Stevens' Patient Oriented Clinical Research Grant (K23 Award), revised submission 7/1/05. If approved, funds from the K23 will be available to offset a portion of the cost of conducting this Follow-up Study. If not approved, NICHD funding has been approved to support the project.

5) Initiation of the Breathing Outcomes Study after enrollment into SUPPORT has begun.

5.1 Babies already enrolled in SUPPORT

To help assure pulmonary outcome assessment for all SUPPORT patients, families of babies already enrolled in SUPPORT will be approached with a separate consent to enroll in the Breathing Outcomes Study. IRB approval of this consent form will be required.

5.2 *Future babies eligible for enrollment in SUPPORT*

Going forward, a modified SUPPORT Consent Form, which includes consent for the Breathing Outcomes Study, will be need to be prepared at each center. The revised SUPPORT Consent will require enrollment into both the SUPPORT Trial and the Breathing Outcomes Study prior to delivery. Because a significant amount of time may elapse between enrollment and the first interview, the Breathing Brochure will be discussed with families, either prior to NICU discharge or within 30 days after NICU discharge.

G.6 Available population/compatibility with other ongoing protocols

Another secondary study proposed by a group independent from ours is looking at the genetics of reactive airways disease in patients enrolled in the SUPPORT Trial. The follow on study proposed here should be complementary to the genetics study, enhancing the both the quality and quantity of data on the prevalence of wheezing and need for outpatient pulmonary care in patients enrolled in the SUPPORT Trial.

G.7 Estimate of projected recruitment time

The recruitment time will be that of the SUPPORT Trial with a 18-22 month period of follow up to ascertain primary and secondary outcomes.

H. RISKS / BENEFITS, WITH ESTIMATE OF FREQUENCY / SEVERITY OF RISKS.

By using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care may be quantified, allowing assessment of whether infants who develop CLD and those who do not have improved pulmonary health as a result of the study intervention. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the follow up visit. We anticipate no risk to the patient of this observational follow on study.

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Subject: Comments for SUPPORT Breathing Outcomes - Follow Up Coordinators Call 11/17
Date: Thursday, November 17, 2005 10:12:24 AM

Dear Participants of today's call,
Please see the email messages below for comments concerning the timing of questionnaire administration and other issues for the Breathing Outcomes Study.

Agenda
Thursday, November 17

2:00-3:00pm Breathing Outcomes
3:00-4:00pm Inositol Cross Sectional Study (Indiana, Yale, Brown, Stanford, Duke, Wake Forest, Rochester)

Dial toll free: **1-888-**[redacted]
Passcode: [redacted]*(then press #)

Thanks, Jamie

Jamie E. Newman, MPH
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-----Original Message-----
From: Roy Heyne [mailto:Roy.Heyne@UTSouthwestern.edu]
Sent: Thursday, November 17, 2005 8:59 AM
To: Newman, Jamie
Cc: ALICIA GUZMAN; JANET MORGAN
Subject: Fwd: Re: SUPPORT Breathing Outcomes - FU Coordinator Call11/17

Jamie, just wanted to be sure you got the e-mail below and had a chance to forward it to the others.

Also wanted to bring up one other issue regarding timing of the 6 and 12 month interviews. According to the manual, these are to be performed at 6 and 12 months corrected age +/- 2-4 weeks. Since all of these infants will be at least 12 weeks (and as much as 16 weeks premature) the interviews would occur around 9-10 months and 15-16 months chronological age, respectively. These ages could coincide with ages sites would otherwise see these children for clinical reasons, though perhaps not as likely as for 6 and 12 months chronological age. In any case, for those sites planning to do these interviews face-to-face, it is important they realize that the study is not budgeted to cover the cost of research visits. So if they cannot take advantage of clinical visit dates, they will need to default to phone interviews.

>>> Roy Heyne 11/15/05 5:04 PM >>>
Jamie, one other question came up with regards to the 18-22 month follow-up, which is actually a component of the primary study , though the Breathing Outcomes secondary adds a questionnaire to it. Granted most of the infants in SUPPORT will be <1000 grams B.W.; but a small percent may be bigger, in

which case they would not be eligible for generic network follow-up. Even if they are eligible, they would need to be separately enrolled in the generic follow-up, in order to qualify for the incentive that we pay for bringing the child back at that time. However, if they are not eligible, it does not appear that either the primary or the secondary offer any incentive for them to return for the 18-22 mo study exam, which might lead to some "selection" bias in follow-up. Furthremore, I think it remains to be seen what sustained level of cooperation we will have with repeated 15-20 minute interviews over the course of 18 months with no incentive beyond good-faith cooperation.

Could you broadcast this to the others who will be participating in the call Thursday, since I think it is something we need to discuss. Thanks.

>>> Roy Heyne 11/14/05 8:16 AM >>>
Thanks for incorporating all the changes we discussed last month. There are a couple of other minor changes I would recommend, and a couple of more significant ones.

1) In Q. 13 on the 6,12,18 month interviews, you might want to add a parenthetical augmentation to "BPD" to cover the alternate description of that disease: "...BPD (or Chronic Lung Disease of Prematurity)..."

2) On 2-5 of the manual, in the revised paragraph about the brochure, would be good to insert language to cover discussion of brochure in the follow-up clinic, for situations where that needs to be an alternative: "...as they leave the NICU or at a follow-up clinic visit..."

3) For questions 9e-g, I had previously raised a question about the gap between "Never" and "Twice a week". While I agree we don't necessarily need to insert an intermediate frequency, I do think you need to broaden the "Never" to "Never or less than twice a week" so we will have some category that fits "once a week" or some other frequency less than 2/wk. (You have done something similar in question 12).

4) On the sample consent, C-2, the last paragraph before "Number of Participants" needs to be omitted, since we have decided to forego the physician chart audit.

From: Petrie, Carolyn
To: adas@rti.org; edward.donovan@chmcc.org; Higgins, Rosemary (NIH/NICHD) [E]; mcw3@cwru.edu; nfiner@ucsd.edu; reverett@med.miami.edu; sduara@miami.edu; wrich@ucsd.edu; wcarlo@peds.uab.edu
Cc: msumner@peds.uab.edu; fmartinez@ucsd.edu; Diane Timmer; wrich@ucsd.edu; Hastings, Betty J.; Zaterka-Baxter, Kristin; Petrie, Carolyn; Poole, W. Kenneth; Gantz, Marie
Subject: Support Call Fri, Nov 18, 12-1pm ET (9-10am PT)
Date: Wednesday, November 16, 2005 4:12:40 PM

The SUPPORT conference call to discuss the use of the SUPPORT study oximeter and performing the physiologic challenge is scheduled for:

Friday, November 18th
12:00-1:00pm ET (9:00-10:00am PT)

To join the call,
Dial Toll Free, **866-675-**(b) (6)
Passcode: (b) (6)

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
CC: 'Avroy A. Fanaroff, M.D.' <aaf2@po.cwru.edu>; 'Betty Hastings' <bkh@rti.org>; 'Ed Donovan' <Edward.Donovan@chmcc.org>; 'Ken Poole' <poo@rti.org>; 'Michele' <mcw3@po.cwru.edu>; 'Neil Finer' <nfiner@ucsd.edu>; 'Shahnaz Duara' <sduara@miami.edu>; 'Wade Rich' <wrich@ucsd.edu>; 'Wally Carlo' <wcarlo@peds.uab.edu>
Sent: Mon Nov 14 18:26:08 2005
Subject: RE: Support question

Hi Rose
This is only an issue for infants still on oxygen. In the course of providing care to any enrolled infant the more frequent scenario is removing an infant from his/her oximeter and then the infant in most units will be placed back on a conventional oximeter. There is so much random noise and differences between any 2 oximeters, that I do not believe that this is an issue. Thus the risk for unblinding is more frequent with the discontinuation of the study oximeter. I am unaware as to whether this has been an issue.
I would recommend that the study oximeter be removed and replaced by an individual who will not do the physiologic challenge, and not by the coordinator, and that an interval of at least 2-4 hours be allowed before the physiologic challenge is performed. There is no urgency to do the physiologic challenge and I believe that an interval of at least 2 -4 hours will be adequate to remove any potential unblinding.
I can be available for a call on Wednesday preferably early my time , between 7:00 and 9:00 AM - your time before 12:00 Noon, and Friday before 12:00 Noon my time. I am in LA Thursday for a CPQCC meeting. However if this day works for the others I would try to be available ideally between 7:30 AM and 9:30 AM.
Let me know
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 14, 2005 3:00 PM

To: edward.donovan@cchmc.org; mcw3@po.cwru.edu; sduara@miami.edu; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: poo@rti.org; adas@rti.org; petrie@rti.org
Subject: Support question

Hi
At the gdb retreat the issue of potential unblinding of oximeters has been raised. If the physiologic challenge is done exactly at 36 weeks and the child's oximeter is changed on that day with a resultant shift up or down in sat levels, the coordinators are concerned that unblinding for that infant and possibly the trial may occur (if the color of the oximeter was known to the staff). We need to have a call this week to discuss this.
Send carolyn your availability for a call this week for
Nov 16
Nov 17
Nov 18

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

From:	Newman, Jamie
To:	Stevens, Timothy; Higgins, Rosemary (NIH/NICHD) [E]; Betty Vohr; maegan.c.currence@uth.tmc.edu; SEguaras@med.miami.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; Janet.Morgan@childrens.com; VPhillips@peds.uab.edu; mgfuller@ucsd.edu; lnoel@wihri.org; ldrichar@iupui.edu; lohme001@mc.duke.edu; bjacksn@wfubmc.edu; diane_hust@urmc.rochester.edu; mbball@leland.stanford.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; ellen_hale@oz.ped.emory.edu; dkennedy@dmc.org; Jackie.Hickman@Childrens.com; bss5@cwru.edu; joanne.williams@yale.edu; Nancy; Rebecca Bara
Cc:	Hastings, Betty J.; Petrie, Carolyn; Das, Abhik; richard.ehrenkranz@yale.edu; jon.e.tyson@uth.tmc.edu; MPeralta@PEDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; apappas@med.wayne.edu; sshankar@med.wayne.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; rdillard@wfubmc.edu; gary_myers@urmc.rochester.edu; bvohr@wihri.org; adusick@iupui.edu; steichji@email.uc.edu; drficmd@aol.com
Subject:	Reminder: SUPPORT Breathing Outcomes - Follow Up Coordinators Call 11/17
Date:	Tuesday, November 15, 2005 3:11:23 PM

Dear Follow-up Coordinators,

The Breathing Outcomes study documents will be discussed on Thursday November 17 from 2-3pm.
The Breathing Brochure was distributed on 11/10 and the Forms, Manual, and Protocol were distributed on 11/3. We anticipate this being the last round of revisions so if you are unable to join the call, please submit your comments by email.

We ask that all Follow Up coordinators join the Breathing Outcomes portion and for Inositol, just the sites participating in the Cross Sectional study. However, all are welcome to join.

Agenda
Thursday, November 17

2:00-3:00pm Breathing Outcomes
3:00-4:00pm Inositol Cross Sectional Study (Indiana, Yale, Brown, Stanford, Duke, Wake Forest, Rochester)

Dial toll free: **1-888-994**(b) (6)
Passcode: [redacted](then press #)

Please let me know if you have any questions.

Thanks, Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From:	Roy Heyne
To:	JACKIE Hickman; JANET MORGAN; bss5@cwru.edu; dkennedy@dmc.org; ldrichar@iupui.edu; mbball@leland.stanford.edu; Higgins, Rosemary (NIH/NICHD) [E]; lohme001@mc.duke.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; SEguaras@med.miami.edu; ellen_hale@oz.ped.emory.edu; VPhillips@PEDS.UAB.EDU; newman@rti.org; Teresa.Gratton@uc.edu; mgfuller@ucsd.edu; diane_hust@urmc.rochester.edu; Timothy_Stevens@urmc.rochester.edu; maegan.c.currence@uth.tmc.edu; bjacksn@wfubmc.edu; npeters@wfubmc.edu; lnoel@wihri.org; elaine.romano@yale.edu; joanne.williams@yale.edu
Cc:	(b) (6) steichji@email.uc.edu; adusick@iupui.edu; golds005@mc.duke.edu; apappas@med.wayne.edu; sshankar@med.wayne.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; MPeralta@PEDS.UAB.EDU; adas@rti.org; bkh@rti.org; petrie@rti.org; srhintz@stanford.edu; yvaucher@ucsd.edu; gary_myers@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; rdillard@wfubmc.edu; bvohr@wihri.org; richard.ehrenkranz@yale.edu
Subject:	Re: SUPPORT Breathing Outcomes - FU Coordinator Call 11/17
Date:	Monday, November 14, 2005 9:17:21 AM

Thanks for incorporating all the changes we discussed last month. There are a couple of other minor changes I would recommend, and a couple of more significant ones.

1) In Q. 13 on the 6,12,18 month interviews, you might want to add a parenthetical augmentation to "BPD" to cover the alternate description of that disease: "...BPD (or Chronic Lung Disease of Prematurity)..."

2) On 2-5 of the manual, in the revised paragraph about the brochure, would be good to insert language to cover discussion of brochure in the follow-up clinic, for situations where that needs to be an alternative: "...as they leave the NICU or at a follow-up clinic visit..."

3) For questions 9e-g, I had previously raised a question about the gap between "Never" and "Twice a week". While I agree we don't necessarily need to insert an intermediate frequency, I do think you need to broaden the "Never" to "Never or less than twice a week" so we will have some category that fits "once a week" or some other frequency less than 2/wk. (You have done something similar in question 12).

4) On the sample consent, C-2, the last paragraph before "Number of Participants" needs to be omitted, since we have decided to forego the physician chart audit.

>>> "Newman, Jamie" <newman@rti.org> 11/03/05 4:33 PM >>>
Dear Follow-up Coordinators,

Attached are the SUPPORT Trial Breathing Outcomes Study documents revised after the call on Tuesday November 1. Due to the confusion with the SUPPORT Follow-up Study and due to IRB concerns with long study titles with multi-syllable words, the title of this study has been changed to the "Breathing Outcomes Study" . We would like to have a call with the coordinators to hear your comments on the Manual and Forms. Several of you have Thursday, November 17 at 2pm already blocked off for the routine NRN Coordinators call. Please let me know if you will be able to join the call from 2-3pm so that we can have a head count of who to expect.

The breathing brochure (formerly the breathing diary) will be distributed to you next week. Please let me know if you have any questions.

Thanks, Jamie

Jamie E. Newman, MPH

Statistics Research Division

RTI International

Telephone: (919) 485-5719

Fax: (919) 485-7762

newman@rti.org

From: Ellen Hale
To: " "Higgins@pales.cc.emory.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT death
Date: Sunday, November 13, 2005 2:25:31 AM

Dear Rose,

We had a death in the del. room of a SuUPPORT infant (cause not related to study). This was rand. (b) (6) We will send the SAE on Wednesday.

Susie and Ellen

From:	Zaterka-Baxter, Kristin
To:	ahensman@wihri.org; mbball@leland.stanford.edu; grisbyca@email.uc.edu; ellen_hale@oz.ped.emory.edu; gaynelle.hensley@utsouthwestern.edu; Georgia E McDavid; auten002@mc.duke.edu; linda_reubens@urmc.rochester.edu; lucmille@iupui.edu; mcollins@peds.uab.edu; monica.konstantino@yale.edu; Nancy.Miller@UTSouthwestern.edu; Nancy Newman; npeters@wfubmc.edu; ae5357@wayne.edu; risa.demetrio@sharp.com; jyhall@stanford.edu; kathy.arnell@sharp.com; Reverett@med.miami.edu; wrich@ucsd.edu; bss5@case.edu; charles.rosenfeld@utsouthwestern.edu; alaptook@wihri.org; [SCRN] Stoll, Barbara; bpoindex@iupui.edu; dale_phelps@urmc.rochester.edu; dstevenson@stanford.edu; edward.donovan@chmcc.org; vanmeurs@leland.stanford.edu; jlemons@iupui.edu; jon.e.tyson@uth.tmc.edu; moshea@wfubmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; goldb008@mc.duke.edu; sshankar@med.wayne.edu; sduara@miami.edu; wcarlo@peds.uab.edu; woh@wihri.org; mcw3@cwru.edu; Walid.Salhab@UTSouthwestern.edu; kurt.schibler@cchmc.org; bsood@med.wayne.edu; balexanba@hotmail.com; Lenora Jackson; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Navarrete, Cristina; gsokol@iupui.edu
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; Hastings, Betty J.; Petrie, Carolyn
Subject:	Growth Secondary to SUPPORT
Date:	Thursday, November 10, 2005 3:59:27 PM
Attachments:	growthprot revised Aug 9 2005.doc GRO-01Nutrition Data[11.10.05]rev1.doc MOP Growth Secondary CN (2).doc

Hi all,
Please find attached the drafted Growth Secondary Protocol, MOP and Form GRO-01 which will be reviewed during the training session next week. Please bring a copy of these materials with you if possible. We will have extra copies available in Savannah.

Thanks and have a save trip.
Kris

Kristin Zaterka-Baxter, RN, BSN, CCRP
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Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study: A Proposed Secondary Study

Cristina Navarrete MD, and Shahnaz Duara MD
University of Miami Miller School of Medicine, Miami, FL.

Abstract:

Post-natal growth restriction is a major problem in preterm infants. Perturbations in oxygenation are recognized to influence post-natal growth; hypoxic conditions can directly impair growth and hyperoxic conditions predispose infants to BPD, which in turn has been linked to poor growth. The NICHD Neonatal Network is conducting a prospective trial of preterm infants randomized to two levels of baseline oxygen saturations. The effect of baseline saturations on pulmonary morbidity and ROP are the primary outcome measures. With respect to post-natal growth, there is a paucity of data relating alterations in baseline oxygen saturation and/or frequent deviations above or below the baseline to growth outcomes. We propose a secondary study to quantify short-term growth velocity in-hospital and long-term growth at 18-22 months of corrected age for infants enrolled in the SUPPORT Trial in relationship to oxygen saturation.

A. Hypothesis to be tested

Primary:

1. Infants in the low oxygen saturation group (85-89%) will have better in-hospital and long-term (18-22 months corrected age) growth.

2. Trajectories of growth in hospital will be better for infants in the low oxygen saturation group.

Secondary:

1. Growth will be greater in infants who spend > 50% of the time with daily median oxygen saturation between 85% -95% while on supplemental oxygen, independent of randomization to low or high oxygen saturation.

2. Infants with BPD will have poorer in-hospital and long-term growth than infants without BPD, independent of the saturation randomization arm.

3. Better long-term growth will be positively related to neuro-developmental outcome, independent of the saturation randomization arm.

B. Specific Aims:

1. To determine anthropometric measurements (wt, HC, length) in infants randomized to low and high oxygen saturation arms, from birth to hospital discharge and again at 18-22 months corrected age.
2. To determine nutritional intake (parenteral and enteral) during hospital stay.
3. To determine the percentage of infants with growth <10 percentile at 36 weeks PMA or discharge, whichever comes first.
4. To determine the percentage of infants with growth <10 percentile at 18-22 months corrected age.
5. To determine growth in relation to the proportion of time spent with oxygen saturation
    a. <85% and >95%
    b. 85%-95%
6. To determine growth in relation to infants' median oxygen saturation while in supplemental oxygen
    a. median oxygen saturation > 95%
    b. median oxygen saturation 85% - 95%
    c. median oxygen saturation < 85%
7. To relate incidence of BPD in low and high saturation arms to growth.
8. To determine in-hospital growth velocity/trajectory in low and high saturation arms.
9. To determine long-term growth velocity/trajectory, from hospital discharge to follow up at 18-22 months corrected age in low and high saturation arms.
10. To relate neuro-developmental outcome at 18-22 months corrected age to long-term growth in low and high saturation arms.

Rationale:

The SUPPORT Trial will randomize infants to two ranges of SpO2 in order to test the hypothesis that use of a lower SpO2 range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity and/or the need for surgical intervention. Retrospective cohort data from several units in the U.K., with different oxygen supplementation policies, revealed poorer growth patterns in the preterm infants exposed to higher oxygen saturations for the duration of oxygen exposure (Tin 2001). Conversely, observational data of infants with established BPD show better growth with home oxygen support (Groothius 1987), and two recent RCT of different target saturations in older oxygen-dependent premature infants showed no difference in short or long-term growth outcomes (STOP-ROP 2000, BOOST Trial 2003). There are no RCT data evaluating the short or long-term growth impact of different SpO2 strategies with supplemental oxygen use in a birth cohort of extremely preterm infants. Therefore, this study provides an opportunity for us to

obtain critically needed growth information on premature infants who are exposed from birth to different target oxygen saturation strategies.

Background

Improvements in antenatal care, respiratory support and nutrition have contributed to increased survival of ELBW infants. As the number of survivors increase, the long term outcome of these infants becomes more important. Lemons et al described growth failure or weight <10th percentile at 36 weeks postmenstrual age in 97% of ELBW infants surviving to discharge. Some morbidities in adulthood are linked to growth during the early post-natal period (Singhal 2004) and make adequacy of growth in this population of heightened interest.

Instead of following intra-uterine growth curves of age matched fetuses, VLBW infants exhibit wide-spread post-natal growth retardation (Cooke 2004), losing ground during the first weeks of life (Berry 1997). To resume growth post-natally, nutrition is of paramount importance; however, other factors such as severity of illness and perhaps oxygenation also play a role. Observational studies of infants with BPD showed poor post-natal growth when infants were sent home without oxygen supplementation (Markestad 1981).

Although preterm infants without lung disease attain oxygen saturations >95%, artificial attempts to keep arterial oxygenation at a "physiological" level may not be beneficial to growth, the lung or retina (Tin 2001). Animal studies have shown that newborn mammals (mice, rats, guinea pigs) develop poor growth with chronic hypoxia and that blunted body growth is directly proportional to the profundity of the exposure to chronic hypoxia (Mortola 1990). Chronic hypoxemia has also been suggested as the cause of poor growth in patients with cyanotic congenital heart disease (Dundar 2000). When home oxygen supplementation was discontinued inappropriately by parents in a cohort of VLBW infants with BPD, there was a deceleration in the rate of weight gain, which improved when oxygen supplementation was resumed (Groothius 1987). Hudak et al in 1989 observed that ELBW infants with CLD who went home on oxygen supplementation had good catch-up growth at 19 months. Taken collectively, these data suggest that hypoxic conditions affect growth negatively and supplementing oxygen may improve growth.

The optimal level of oxygen saturation to promote post-natal growth is unknown. Most of the available human data is limited to oxygen supplementation of infants who are oxygen dependent or have BPD. Baraldi et al demonstrated that discharged infants with BPD, who were kept on supplemental oxygen to keep saturations above 94%, had progressive but poor weight gain (stayed below 3rd percentile) at 9 months corrected age follow-up. In infants with BPD whose oxygen supplementation was intentionally discontinued, the subset who exhibited episodes of desaturations below 88-91% had a significant decline in the rate of weight gain as compared to those who maintained saturations above 92% (Moyer-Mileur 1996). Conversely, when two different oxygen saturation control policies (high: 88-98% and low: 70-90%) were retrospectively reviewed in <28

week gestation infants, the infants being cared for in the high oxygen saturation policy units were more likely to weigh less than the 3rd percentile at discharge (45% vs. 17%, Tin 2001). The infants assigned to the high oxygen saturation limits were also more likely to have BPD and ROP.

Recently, the BOOST Trial demonstrated that randomizing infants born <30 weeks gestation who were still on oxygen at 32 weeks postmenstrual age either to standard saturations (91-94%) or to high saturations (95-98%) produced no significant difference in growth at 12 months corrected age. This study, while randomizing infants to two different levels of saturations (conventional and high), only enrolled infants if they were still on oxygen supplementation at 32 weeks PMA and used higher limits than planned by SUPPORT. Our proposal is novel in that randomization to the two oxygen strategies begins at birth and continues for as long as the infants are in supplemental oxygen - by implementing this secondary we will be able to determine the impact of these strategies on short and long-term growth.

Methods:

Anthropometric Measures – at birth, postnatal days 7, 14, 21, and 28 days, 32 w PMA and 36 w PMA or discharge (wt, length, HC)

1. Weight - using standard digital electronic scales (c/o infant's nurse)
2. Length - using the Premie Length Board (average of two values, c/o research staff)
3. Head circumference - using paper measurement tape (average of c/o research staff)

Clinical Data-

1. Date when infant regains birth weight
2. Date of first enteral feed
3. Date of full enteral feeds (enteral > 120ml/kg/d)
4. Total number of days on parenteral nutrition
5. 24 h intake 'snapshots' (Parenteral, Enteral) – postnatal days 7, 14, 21, and 28, 32w PMA, 36w PMA or discharge (whichever comes first)
6. Presence of BPD

Intervention Data –

1. Duration of time spent in target saturation ranges of interest (Already part of SUPPORT‡)
2. Median values for unmasked oxygen saturation while still on supplemental oxygen therapy‡
3. Highest daily FiO_2‡
4. Duration of supplemental oxygen exposure‡
5. Documentation of post-discharge oxygen use

Follow Up data –

1. Anthropometric measurements at 18-22months corrected age
2. Neuro-developmental follow up at 18-22 months corrected age

Primary Outcome:

Growth in-hospital and at 18-22 months corrected age and in-hospital growth trajectories in high and low saturation arms.

Sample Size:

Given the importance of using an RCT to establish the impact of different levels of oxygen saturation from birth on short and long term growth, and recognizing the wealth of oxygen saturation data that will be available for analysis combined with the absence of comparable data in the literature, all infants in the SUPPORT Trial should be recruited into this secondary (n=1320). This sample size will be adequate to detect subtle differences in growth between the two groups with adequate ($\geq$80%) power. For example, this sample size will have at least 80% power to detect a difference in means between the two saturation groups of less than 40 g (assuming a mean weight of 1000 g in the control group and a standard deviation of 250 g) using a two group t-test with a 0.05 two-sided significance level.

Statistical Analysis:

Based upon intent-to-treat, differences between treatment arms with respect to continuous outcomes (such as weight, length, etc.) will be assessed by the Student t-test or the Mann-Whitney U-test, depending upon whether the empirical distribution of the data is approximately normal or heavily skewed. Adjusted analyses will be conducted using linear regression to determine the relationship between measures of oxygen saturation and growth in the presence of covariates and confounders (such as site, gestational age, gender, etc.). Categorical outcomes (such as BPD, growth failure, etc.) will be compared across treatment groups using the chi-square test. Logistic regression models will be developed to determine whether oxygen saturation independently affects growth after correction for confounding variables that also alter growth.

In-hospital growth data will be available over multiple points in time. Outcomes available from this temporal distribution will enable us to perform a longitudinal analysis comparing the trajectories of growth between the two treatment groups. Longitudinal studies are powerful both in terms of explanatory power and statistical efficiency. They are useful in examining whether children in the two different oxygen saturation arms have different developmental trajectories over time. Further, longitudinal studies are statistically more efficient since they acknowledge and account for naturally occurring differences among children, including unmeasured characteristics such as genetic make-up, prenatal exposures, etc.

In order to analyze longitudinal growth data we propose to use hierarchical modeling, where the first stage models growth as a function of time/child's age, and the second stage models this association as a function of each child's

treatment status. This flexible modeling formulation allows each child to have its own unique developmental trajectory, which could depend on its treatment status.

Discussion of Anticipated Results

We anticipate a better growth outcome in-hospital and at 18-22 months corrected age in the infants randomized to the lower target saturation range who maintained their median oxygen saturations within study range. We further anticipate that longitudinal analyses will demonstrate that these infants will have a sustained higher trajectory of growth over time compared to infants in the higher target saturation range.

Budget:

Additional nursing time, needed to collect required anthropometric data and other data from chart review at discharge and at follow-up, is estimated to be 1 hour. The cost for the entire cohort (1320 subjects), at $32.00 per nursing hour, would be $42,220. Assuming a 35% mortality for this extremely preterm population (estimated from GDB), 858 subjects could be expected to survive to discharge and estimating time for survivors alone will reduce the budget to $27,456.00.

References:

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This form should be completed on day of life 1, 7, 14, 21 and 28, corrected ages 32 weeks and 36 weeks or discharge. Data should be collected for each time point (± I day).

1. Date: __ __ /__ __ /__ __ __ __ (Month / Day / Year) **2. Day of Life:** __ __ __

3. Is the infant medically stable to obtain anthropometrics Y N

If yes,

4. Today's New Weight (gms): __ __ __ __

5. Today's New Length (cm): __ __ . __

6. Today's New Head Circumference (cm): __ __ . __

A. PARENTERALNUTRITIONAL INTAKE

1. Was there parenteral Intake? Y N

If Yes,

2. PN	**% Dextrose**	**AA Ordered (gm/kg/d)**	**PN Volume Received (cc's)**	**% Lipid Solution**	**Intralipid Volume Received (cc's)**
a. Today's 1st Bag	__ __ . __	__ . __	__ __ __ . __	__ __	__ __ . __
b. Today's 2nd Bag	__ __ . __	__ . __	__ __ __ . __	__ __	__ __ . __
c. Today's 3rd Bag	__ __ . __	__ . __	__ __ __ . __	__ __	__ __ . __

B. ENTERAL INTAKE

1. Was there enteral Intake? Y N

a. If Yes, record information below:

	Type	**Caloric Density (Kcal/ounce)**	**Volume Received (cc's)**	**Nutrient Additives**
1.	__ __ __	__ __	__ __ __ . __	__ __ __ __
2.	__ __ __	__ __	__ __ __ . __	__ __ __ __
3.	__ __ __	__ __	__ __ __ . __	__ __ __ __
4.	__ __ __	__ __	__ __ __ . __	__ __ __ __

Enteral Nutrition Key

Type:	Nutrient Additives:
00= none 01= breast milk (full strength) 02= Similac Special Care 03= Enfamil Premature Formula 04= Similac (regular term infant formula) 05= Enfamil (regular term infant formula) 06= Pregestimil 07= Nutramigen 08= Alimentum 09= Prosobee 10= Isomil 11= Similac 60/40 12= Similac Natural Care 13= Neosure 14= Enfamil 22 15= Other 16= Pedialyte	2= MCT or other oil 4= polycose 6= human milk fortifier 8= formula powder or liquid 9= Promod 7= other

Initials of person completing this form: ___ ___ ___

Manual of Operations for the NICHD Neonatal Research Network

Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study

Draft
November 10, 2005

Table of Contents

Chapter 1

Objectives and Trial Design

1.1 Introduction

This manual provides detailed instructions for the secondary study of *Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study.* The manual is meant to serve as a reference guide for study staff including investigators, coordinators and data managers. The trial objectives and design are summarized briefly below. For further discussion of the study background and design, please refer to the protocol.

1.2 Trial Hypotheses

Post-natal growth restriction is a major problem in preterm infants. Perturbations in oxygenation are recognized to influence post-natal growth; hypoxic conditions can directly impair growth and hyperoxic conditions predispose infants to BPD, which in turn has been linked to poor growth. The NICHD Neonatal Network is conducting a prospective trial of preterm infants randomized to two levels of baseline oxygen saturations. The effect of baseline saturations on pulmonary morbidity and ROP are the primary outcome measures. With respect to post-natal growth, there is a paucity of data relating alterations in baseline oxygen saturation and/or frequent deviations above or below the baseline to growth outcomes. We propose a secondary study to quantify short-term growth velocity in-hospital and long-term growth at 18-22 months of corrected age for infants enrolled in the SUPPORT Trial in relationship to oxygen saturation.

1.2.1 Primary Hypothesis:

1. Infants in the low oxygen saturation group (85-89%) will have better in-hospital and long-term (18-22 months corrected age) growth.

2. Trajectories of growth in hospital will be better for infants in the low oxygen saturation group.

1.2.2 Secondary Hypothesis:

1. Growth will be greater in infants who spend > 50% of the time with daily median oxygen saturation between 85% -95% while on supplemental oxygen, independent of randomization to low or high oxygen saturation.

2. Infants with BPD will have poorer in-hospital and long-term growth than infants without BPD, independent of the saturation randomization arm.

3. Better long-term growth will be positively related to neuro-developmental outcome, independent of the saturation randomization arm.

1.3 Specific Study Aims

a. To determine anthropometric measurements (wt, HC, length) in infants randomized to low and high oxygen saturation arms, from birth to hospital discharge and again at 18-22 months corrected age.
b. To determine nutritional intake (parenteral and enteral) during hospital stay.
c. To determine the percentage of infants with growth <10 percentile at 36 weeks PMA or discharge, whichever comes first.
d. To determine the percentage of infants with growth <10 percentile at 18-22 months corrected age.
e. To determine growth in relation to the proportion of time spent with oxygen saturation
    1. <85% and >95%
    2. 85%-95%
f. To determine growth in relation to infants' median oxygen saturation while in supplemental oxygen
    1. median oxygen saturation > 95%
    2. median oxygen saturation 85% - 95%
    3. median oxygen saturation < 85%
g. To relate incidence of BPD in low and high saturation arms to growth.
h. To determine in-hospital growth velocity/trajectory in low and high saturation arms.
i. To determine long-term growth velocity/trajectory, from hospital discharge to follow up at 18-22 months corrected age in low and high saturation arms.
j. To relate neuro-developmental outcome at 18-22 months corrected age to long-term growth in low and high saturation arms.

1.4 Study Design

This is an Observational Secondary study to the SUPPORT trial. Anthropometric measurements, clinical data, interventional data and follow-up data will be collected at .

1.4.1 Anthropometric Measures

Weight, length and head circumference will be measured at birth, postnatal age 7, 14, 21, and 28 days, 32 weeks postmenstrual age and 36 weeks postmenstrual age or discharge which ever comes first.

1. Weight – using standard digital electronic scales (c/o infant's nurse)
2. Length – using the Premie Length Board (average of two values, c/o research staff)
3. Head circumference – using paper measurement tape (average of c/o research staff)

1.4.2 Clinical Data

1. Date when the infant regains birth weight.
2. Date of first enteral feed.
3. Date of full enteral feed > 120ml/kg/d.
4. Total number of days on parenteral nutrition.
5. 24 hour intake 'snapshots' (parenteral, enteral) – postnatal age 7, 14, 21, and 28 day, 32 weeks postmenstrual age and 36 weeks postmenstrual age or discharge which ever comes first.
6. Presence of BPD.

1.4.3 Intervention Data

1. Duration of time spent in target saturation ranges of interest (already part of SUPPORT[‡]).
2. Median values for unmasked oxygen saturation while still on supplemental oxygen therapy[‡].
3. Highest daily FiO_2[‡].
4. Duration of supplemental oxygen exposure[‡].
5. Documentation of post-discharge oxygen use.

1.4.4 Follow Up data

1. Anthropometric measurements at 18-22months corrected age.
2. Neuro-developmental follow up at 18-22 months corrected age.

1.5 Sample Size

Given the importance of using an RCT to establish the impact of different levels of oxygen saturation from birth on short and long term growth, and recognizing the wealth of oxygen saturation data that will be available for analysis combined with the absence of comparable data in the literature, all infants in the SUPPORT Trial as of the start date of the secondary should be recruited **(n=1320)**. This sample size will be adequate to detect subtle differences in growth between the two groups with adequate (≥80%) power. For example, this sample size will have at least 80% power to detect a difference in means between the two saturation groups of less than 40 g (assuming a mean weight of 1000 g in the control group and a standard deviation of 250 g) using a two group t-test with a 0.05 two-sided significance level.

1.6 Study Outcomes

1.6.1 Primary Outcome

Growth in-hospital and at 18-22 months corrected age and in-hospital growth trajectories in high and low saturation arms.

Chapter 2

Administration

2.1 Organizational Structure

Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study is being conducted by the NICHD Neonatal Research Network. The Network is funded by the NICHD under cooperative agreements with sixteen institutions comprised of twenty clinical centers and a data coordinating center. The Steering committee for the Network consists of the Principal Investigator from each clinical center, the data center, and the NICHD project officer. The Steering Committee Chairman is appointed by NICHD and is not a Principal Investigator from any of the Clinical Centers. The Post-natal Growth Secondary Protocol Subcommittee is responsible for the preparation and maintenance of the protocol, data forms, and manual of operations. This subcommittee will monitor the overall study performance (including protocol compliance) and will report the progress of the trial to the Steering Committee. The Post-natal Growth subcommittee members are:

Cristina Navarrete
Shahnaz Duara
Richard A. Ehrenkranz
Ruth Everett
Neil Finer
Brenda Poindexter
Abhik Das
Rosemary Higgins

2.2 Participating Centers

Centers from the NICHD Neonatal Research Network participating in the trial are listed with NICHD center numbers in parenthesis and principal investigators listed in the right column.

PARTICIPATING CENTERS	NRN PI	SUPPORT STUDY PI
Case Western Reserve Univ. (3) Rainbow Babies and Children's Hospital	Michele Walsh, MD	Michele Walsh, MD
University of Texas-Dallas (4)	Charles Rosenfeld, MD	Walid Salhab, MD
Wayne State University (5) Children's Hospital of Michigan	Seetha Shankaran, MD	Seetha Shankaran, MD
University of Miami (8) Jackson Memorial Hospital	Shahnaz Duara, MD	Cristina Navarrete MD
Emory University (9) Grady Memorial Hospital	Barbara J. Stoll, MD	Susie Buchter, MD
University of Cincinnati (11) University of Cincinnati Hospital	Edward F. Donovan, MD	Vivek Narendran, MD Kurt Schibler, MD
Indiana University (12)	James A. Lemons, MD	Brenda Poindexter, MD

Yale University (13) The Children's Hospital at Yale – New Haven	Richard A. Ehrenkranz, MD	Vineet Bhandari, MD
Brown University (14) Women and Infant's Hospital	William Oh, MD	Abbot Laptook, MD
Stanford University (15) Stanford University Med Center	David K. Stevenson, MD	Krisa Van Meurs, MD
University of Alabama (16) University of Alabama at Birmingham	Waldemar A. Carlo, MD	Waldemar A. Carlo, MD
University of Texas- Houston (18)	Jon E. Tyson, MD	Brenda Morris, MD
Duke University (19)	Ronald Goldberg, MD	C. Michael Cotten, MD
Wake Forest University (20)	Michael O'Shea, MD	Michael O'Shea, MD
Children's Hospital at Strong (21)	Dale L. Phelps, MD	Nirupama Laroia, MD
University of California-San Diego (22)	Neil Finer, MD	Neil Finer, MD

2.3 Responsibilities of the Clinical Centers

The minimum staff required for network participation at each clinical center is the physician Principal Investigator (PI), the Research Coordinator and/or research nurse. The responsibilities of these individuals are described briefly in this chapter.

The **PI** or designee is responsible for ensuring the proper conduct of the trial at his or her clinical center (including recruitment and treatment of patients as specified in the protocol), accurate collection of data and transmission of information to the Data Coordinating Center (DCC). Other specific duties include the following:

- Presenting an in-service to the other physicians
- Applying for IRB approval
- Introducing the study to the parents of prospective patients, and obtaining signed informed consent from the parents of eligible infants (in some centers this responsibility may be delegated)
- Reviewing all infants for whom informed consent has been obtained to confirm their eligibility
- Informing the IRB of the study progress.

The **Research Coordinator** will be responsible for the day-to-day operations of the study at the clinical center, including data collection and management. This responsibility includes the following:

- Presenting an in-service to the appropriate nursing and ancillary staff and respiratory therapists detailing the study protocol
- Collecting information necessary to complete the data collection forms, and coordinating data entry
- Training and certifying the staff in the use of the network microcomputer

- Controlling access to the network microcomputer and ensuring that required back-up, security and confidentiality are maintained
- Responding to edit messages and other communications from the data enter
- Distributing updates of the protocol and of the manual of operations to clinical center staff
- Reporting protocol deviations (including unmasking) by monitoring the respiratory therapy worksheets

The pharmacist/research nurse will be responsible for randomizing the patient using a randomization list kept at each site.The pharmacist will be responsible for reconstituting the study drug for nebulization. Each infant will be monitored for adequate study drug (aerosol) delivery and for possible toxicity. The responsibilities of the pharmacist/research nurse and the respiratory therapist include the following:

- Developing strategies to maintain masking in cooperation with the PI
- Achieving and maintaining fluency with the procedures for obtaining the treatment group assignment from the data center
- Maintaining the study equipment to facilitate rapid set up and connection, minimizing the time between randomization and initiation of study aerosol.
- Monitoring the infant for signs of toxicity
- Monitoring the study aerosol administration and scavenging equipment for potential environmental contamination
- Completing the safety information and submitting it to the data center within 48 hours of study aerosol discontinuation
- Monitoring adherence to the protocol with respect to study aerosol management, and reporting deviations to the data center within 24 hours of occurrence

2.4 Responsibilities of the Data Coordinating Center

The DCC is responsible for all aspects of statistical design and analysis as well as data management of the study. In particular, this includes:

- Processing, updating and distributing the protocol and manual of operations
- Developing, printing and distributing the data forms, including periodic updates as necessary
- Developing, testing and implementing the database and other software. Ensuring that data are correct and complete by implementing editing and auditing procedures
- Monitoring the progress and quality of the study
- Preparing interim and final analyses and reports
- Participating in the preparation of presentations and publications relating to the study.

2.5 Responsibilities of NICHD

In addition to its role as a funding agency, the NICHD participates in the activities of the cooperative agreement by being represented on the Steering Committee. The Program Official also participates in the development of protocol and in assisting the Steering committee in the coordination of the studies conducted by the Network. The NICHD Program Official, in conjunction with the RTI Principal Investigator is responsible for monitoring site performance of all participating centers. The Program Official has the following responsibilities:

- Assistance in the development of the study protocol.
- Assistance in the development of capitation-based budgets, including the identification of study costs and special institutional needs.
- Allocation of network resources to meet study needs including pharmacies, study drug supply, and other special requirements of the study.
- Facilitation of training meetings, site visits, and subcommittee meetings.
- Participating in preparation of publications.

Chapter 3

Study Forms

3.1 Nutritional Intake Form: (GRO-01)

This form will be completed on all enrolled infants on days 1, 7 (±1d), 14 (±1d), 21 (±1d) and 28 (±1d), and on postmenstrual age 32 and 36 weeks or discharge whichever comes first. Plus/minus one day (±1) will entail assessing infant 24 hours before actual data collection day for severity of illness as per clinical team (attending, fellow, or nurse) that would preclude anthropometric measurements. If the infant is too ill for measurements, re-assessments are to be made for the next 48 hours.

3.1.1 Instructions for Completing Form GRO-01 (Nutritional Intake Form)

- **Center Number**
  Each study center has been assigned a Network center number.

- **Site**
  The center assigns these to their various hospitals. If applicable, any site letter or number is acceptable.

- **Network Number**
  The Network number is made up of a four digit Family (Pregnancy) Number plus the Birth Order Number. Therefore the Network Number is 5 digits.

- **Birth Number**
  This code distinguishes between siblings in the NICU. A single birth or first born of a multiple birth will be coded '1', '2', etc. It does not necessarily have to conform to strict birth order from a multiple birth, but must be kept consistent for each baby.

- **Mother's Initials**
  The Mother's normal initials (first, middle and last). If there is **no** middle initial, record the two initials. **This information is optional.**

- **Report Number**
  The Report Number is a sequential number, starting with number 1, documenting the number of times this form has been completed. (i.e., DOL 1 = report number 1; DOL 7 = report number 2 etc.)

1. Date
Record the date in MM/DD/YYYY format in which the day of life and the information correspond.

2. Day of life
Day one of life is the day that the baby is born. All data will be entered under the corresponding day of life.

3. Is the infant medically stable to obtain anthropometrics?
If yes, continue to #4
If no, re-assess within the next 48 hours for clinical stability. If deemed unstable for handling by the end of the 48 hour time frame, leave the space for the unavailable anthropometric measurements marked by *.

4. Today's New Weight
Document weight in grams as recorded by the bedside nurse.

5. Today's New Length
Document length in centimeters, rounded off to the nearest tenth. Measurements should be obtained by the research staff using the Premie Length Board, the infant is placed supine on the board (without a diaper). One examiner holds the infant's head horizontal and aligned to the spine so that there is no lateral tilt of the head or rotation of the chin from the midline. Gentle traction is applied to bring the top of the head into contact with the fixed headboard. The second examiner holds the infant's feet, toes pointing directly upward, and applies gentle traction to straighten the legs. The moveable footboard is brought to the feet and a measurement is taken when it is pressed firmly against the infant's heels. The length must be documented to the nearest tenth. Two measurements are taken and if they are within 1 cm of each other, the average is recorded. If the measurements are not within 1 cm of each other, a third measure should be taken and the median of the three is recorded.

6. Today's New Head Circumference
Document head circumference in centimeters rounded off to the nearest tenth. Measurements should be obtained by the research staff by applying a measuring tape firmly around the head above the supraorbital ridge (most prominent part of the forehead), and over the occiput to give the maximum circumference. Two measurements should be taken, if the measurements are within 0.5 cm of each other, record the average. If they are not within 0.5 cm of each other, a third measure should be taken and the median of the three should be recorded (to the nearest tenth).

SECTION A. PARENTERAL NUTRITIONAL INTAKE

1. Was there parenteral intake?
If yes, complete question 2

2. For each 24-hour period record the following information for each bag of parenteral nutrition.

- Percent dextrose: Record the percent dextrose solution of the given bag of parenteral nutrition
- Amino acids: Record the number of grams/kg/day of amino acids ordered by the physician for this bag of parenteral nutrition (record to the nearest tenth) OR record the concentration of amino acids in grams per liter in a given bag
- Record PN volume received: Enter the volume in cc of parenteral nutrition the infant received from the given bag during the 24 hour period
- Intralipids: Enter the percent solution used (10 or 20%) and the total volume in cc of intralipids that the infant received during the same 24 hour period

SECTION B. ENTERAL INTAKE

1. Was there enteral intake?
If yes, record the following for each:

- Type:
  Record the type code from the Enteral Nutrition Key table (found at the bottom right corner of the form), corresponding to the type given during the 24 hour period. If infant was NPO for the 24 hour time period, record "00" and the remainder of this section should be left blank for the given day
- Caloric Density:
  Document the total caloric density per ounce of the feeding type given. See Appendix.
- Volume received:
  Record the total amount of the particular feeding type given in the 24 hour time period (in cc's to the tenth).
- Nutrient additives:
  Use the codes listed in the Enteral Nutrition Key table to document the use of MCT or other oil, Polycose, human milk fortifier, or liquid or powder formula added to the feeding.

APPENDIX A

Caloric density:

Milk Formula	Full strength (kcal/oz)	½ strength (kcal/oz)
Expressed breast milk Enfamil Premature Formula 20 Similac Special Care 20 Pregestimil 20 Nutramigen Similac 60/40 Isomil/ProSobee Alimentum Neocate	20	10
Enfamil Premature Formula 24 Similac Special Care 24 Pregestimil 24	24	12
Neosure Enfamil 22 (Enfacare)	22	11
Pedialyte	3	

From: Zaterka-Baxter, Kristin
To: richard.ehrenkranz@yale.edu; sduara@miami.edu; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Brenda Poindexter
Cc: Navarrete, Cristina; Everett, Ruth; Hastings, Betty J.
Subject: FW: SUPPORT Growth Secondary
Date: Tuesday, November 01, 2005 9:05:01 AM
Attachments: Agenda for Support Trial.doc

Dear all,

Attached please find an agenda from Dr. Navarrete for the Support Growth secondary conference call. As a reminder, this call is scheduled for today, Tuesday, November 1st, 2005 from 1:00 - 2:00pm EST (10:00-11:00am PST).

Dial Toll free: 888-994(b) (6)

Pass code: (b) (6)(# when prompted)

Thanks,
Kris

Kristin Zaterka-Baxter
RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

Agenda
Support Trial: Growth Secondary Conference call
November 1, 2005; 1-2pm

1. Discussion of the GRO-01 data form
2. Training and data collection for SUPPORT patients already enrolled
3. Dr. Tyson's queries
4. Any other issues related to the Growth secondary

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: RE: SUPPORT AEs
Date: Thursday, November 10, 2005 1:27:46 PM

Thanks for the clarification. We will bring anything of potential concern to the DSMC.

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, November 10, 2005 1:25 PM
To: Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT AEs

Marie and Abhik
I just wanted to make sure that we are following nasal breakdown. If things are ok within the groups, it is fine. If there is an excessive incidence in one group – that should be referred to the DSMC.

Thanks
Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, November 10, 2005 1:11 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: FW: SUPPORT AEs

Rose:

Please see question from Marie below.

Thanks

Abhik

-----Original Message-----
From: Gantz, Marie
Sent: Thursday, November 10, 2005 1:03 PM
To: Das, Abhik
Subject: RE: SUPPORT AEs

Hi Abhik,

Nasal breakdown is one of the outcomes we currently look at, in combination with other AEs. Does she want to look at that event separately?

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International

P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone (919) 485-7780
Fax (919) 485-7762
mgantz@rti.org

-----Original Message-----
From: Das, Abhik
Sent: Thursday, November 10, 2005 12:38 PM
To: Gantz, Marie
Subject: SUPPORT AEs

Marie:

Rose thinks we ought to look at Nasal breakdown requiring discontinuation of nasal prongs by treatment group as well when we do our periodic safety looks.

Thanks

Abhik

Abhik Das, Ph.D.
Senior Research Statistician

RTI International
6110 Executive Blvd., Suite 902
Rockville, MD 20852-3903
e-mail: adas@rti.org
Phone: 301-770-8214
Fax: 301-230-4646

From: Newman, Jamie
To: Stevens, Timothy; Higgins, Rosemary (NIH/NICHD) [E]; Betty Vohr; maegan.c.currence@uth.tmc.edu; SEguaras@med.miami.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; Janet.Morgan@childrens.com; VPhillips@peds.uab.edu; mgfuller@ucsd.edu; lnoel@wihri.org; ldrichar@iupui.edu; lohme001@mc.duke.edu; bjacksn@wfubmc.edu; diane_hust@urmc.rochester.edu; mbball@leland.stanford.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; ellen_hale@oz.ped.emory.edu; dkennedy@dmc.org; Jackie.Hickman@Childrens.com; bss5@cwru.edu; joanne.williams@yale.edu; Nancy; Rebecca Bara
Cc: Hastings, Betty J.; Petrie, Carolyn; Das, Abhik; richard.ehrenkranz@yale.edu; jon.e.tyson@uth.tmc.edu; MPeralta@PEDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; apappas@med.wayne.edu; sshankar@med.wayne.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; rdillard@wfubmc.edu; gary_myers@urmc.rochester.edu; bvohr@wihri.org; adusick@iupui.edu; steichji@email.uc.edu; drfjcmd@aol.com
Subject: SUPPORT Breathing Outcomes - FU Coordinator Call 11/17
Date: Thursday, November 10, 2005 9:42:42 AM
Attachments: Breathing Brochure11_10.doc

Dear Follow-up Coordinators,

Attached is the Breathing Brochure (formerly the Breathing Diary, which has been shortened). This along with the study documents distributed to you on 11/3 (Forms, Manual, and Protocol) will be discussed on Thursday November 17 from 2-3pm.

We ask that all Follow Up coordinators join the Breathing Outcomes portion and for Inositol, just the sites participating in the Cross Sectional study. However, all are welcome to join.

Agenda
Thursday, November 17

2:00-3:00pm Breathing Outcomes
3:00-4:00pm Inositol Cross Sectional Study (Indiana, Yale, Brown, Stanford, Duke, Wake Forest, Rochester)

Dial toll free: **1-888-994**(b) (6)
Passcode: (b) (6) (then press #)

Please let me know if you have any questions.

Thanks, Jamie

Jamie E. Newman, MPH
Statistics Research Division
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Newman, Jamie
Sent: Thursday, November 03, 2005 5:33 PM
To: Stevens, Timothy; 'higginsr@mail.nih.gov'; 'Betty Vohr'; 'maegan.c.currence@uth.tmc.edu'; 'SEguaras@med.miami.edu'; 'MNeri@med.miami.edu'; 'Reverett@med.miami.edu'; 'Janet.Morgan@childrens.com'; 'VPhillips@peds.uab.edu'; 'mgfuller@ucsd.edu'; 'lnoel@wihri.org'; 'ldrichar@iupui.edu'; 'lohme001@mc.duke.edu'; 'bjacksn@wfubmc.edu'; 'diane_hust@urmc.rochester.edu'; 'mbball@leland.stanford.edu'; 'elaine.romano@yale.edu'; 'Teresa.Gratton@uc.edu'; 'ellen_hale@oz.ped.emory.edu'; 'dkennedy@dmc.org'; 'Jackie.Hickman@Childrens.com'; 'bss5@cwru.edu'; 'joanne.williams@yale.edu'; Nancy
Cc: Hastings, Betty J.; Petrie, Carolyn; Das, Abhik; richard.ehrenkranz@yale.edu; jon.e.tyson@uth.tmc.edu; MPeralta@PEDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; ira_adams-

chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; apappas@med.wayne.edu; sshankar@med.wayne.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; rdillard@wfubmc.edu; gary_myers@urmc.rochester.edu; bvohr@wihri.org; adusick@iupui.edu; steichjj@email.uc.edu; (b) (6)

Subject: SUPPORT Breathing Outcomes - FU Coordinator Call 11/17

Dear Follow-up Coordinators,

Attached are the SUPPORT Trial Breathing Outcomes Study documents revised after the call on Tuesday November 1. Due to the confusion with the SUPPORT Follow-up Study and due to IRB concerns with long study titles with multi-syllable words, the title of this study has been changed to the "Breathing Outcomes Study" . We would like to have a call with the coordinators to hear your comments on the Manual and Forms. Several of you have Thursday, November 17 at 2pm already blocked off for the routine NRN Coordinators call. Please let me know if you will be able to join the call from 2-3pm so that we can have a head count of who to expect.

The breathing brochure (formerly the breathing diary) will be distributed to you next week. Please let me know if you have any questions.

Thanks, Jamie

Jamie E. Newman, MPH
Statistics Research Division
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

NOTES

Thank you for participating.

Breathing Study Brochure

Golisano Children's Hospital at Strong

University of Rochester

Created for:

Born:

Birth Weight:

Length:

Home from NICU:

Neonatal Continuing Care Program
At Golisano Children's Hospital at Strong

PO Box 651
601 Elmwood Avenue
Rochester, NY 14642

Telephone: (585) 275-8373

NICHD NEONATAL RESEARCH NETWORK

NICHD SUPPORT Trial
Breathing Study

Premature babies are more likely than full term babies to have breathing problems after discharge from the NICU. The purpose of this study is to see whether the treatment your baby received as part of the SUPPORT Study improves your baby's breathing in the 18-22 months following the baby's due date.

As part of this study, we will contact you every 6 months or so to ask you questions about your baby's breathing. The questions will be about your baby's breathing symptoms, especially wheezing and coughing, and about your baby's need for medical visits and treatments for breathing problems.

Wheezing can mean different sounds to different people. By wheezing, we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical.

To help us understand your baby's breathing, please note how often your baby has wheezing or coughing, whether your baby visited a doctor's office, emergency room or was hospitalized for breathing problems and what medications your baby needs.

Feel free to use the back of this brochure, a calendar or another sheet to make notes that help you keep track of your baby's breathing.

When we call, we'd like you to gather any notes, medications or other information about your baby's breathing. As with all information we collect, the answers to these questions will be kept confidential.

From: Mcdavid, Georgia E
To: Hastings, Betty J.; Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn; Zaterka-Baxter, Kristin
Subject: SUPPORT death
Date: Monday, November 07, 2005 1:26:44 PM

Infant GDB(b) (6)1 DOB (b) (6) expired (b) (6) due to NEC. Death appears unrelated to the study.

From:	Newman, Jamie
To:	Stevens, Timothy; Higgins, Rosemary (NIH/NICHD) [E]; Betty Vohr; maegan.c.currence@uth.tmc.edu; SEguaras@med.miami.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; Janet.Morgan@childrens.com; VPhillips@peds.uab.edu; mgfuller@ucsd.edu; lnoel@wihri.org; ldrichar@iupui.edu; lohme001@mc.duke.edu; bjacksn@wfubmc.edu; diane_hust@urmc.rochester.edu; mbball@leland.stanford.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; ellen_hale@oz.ped.emory.edu; dkennedy@dmc.org; Jackie.Hickman@Childrens.com; bss5@cwru.edu; joanne.williams@yale.edu; Nancy
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Subject:	SUPPORT Breathing Outcomes - FU Coordinator Call 11/17
Date:	Thursday, November 03, 2005 5:33:24 PM
Attachments:	SUPPORT BO Protocol 11-3.doc SUPPORT BO Forms 11-3.doc SUPPORT BO Manual11-3.doc

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Dear Follow-up Coordinators,

Attached are the SUPPORT Trial Breathing Outcomes Study documents revised after the call on Tuesday November 1. Due to the confusion with the SUPPORT Follow-up Study and due to IRB concerns with long study titles with multi-syllable words, the title of this study has been changed to the "Breathing Outcomes Study" . We would like to have a call with the coordinators to hear your comments on the Manual and Forms. Several of you have Thursday, November 17 at 2pm already blocked off for the routine NRN Coordinators call. Please let me know if you will be able to join the call from 2-3pm so that we can have a head count of who to expect.

The breathing brochure (formerly the breathing diary) will be distributed to you next week. Please let me know if you have any questions.

Thanks, Jamie

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NICHD SUPPORT Trial
Breathing Outcomes Study

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Proposal Updated: November 1, 2005

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Study Protocol

ABSTRACT

Statement of Problem Premature infants have a greater risk of recurrent wheezing and chronic cough and greater need for pulmonary care in early childhood than term infants (1-11). Although Chronic Lung Disease (CLD) is a risk factor, the etiology of symptomatic airway dysfunction, defined hereafter as recurrent wheezing and/or chronic cough, in formerly premature infants is not known.

Hypotheses The goal of this clinical project is to understand better the antecedents of symptomatic airway dysfunction among preterm infants during early childhood by evaluating the effect of treatment with different levels of targeted oxygen saturation in the immediate neonatal period. **The overarching hypothesis is that premature infants exposed to supplemental oxygen suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction and respiratory symptoms when challenged with subsequent environmental or infectious exposures.**

Hypothesis #1- Relative to infants managed with a higher SpO2 range, infants who are managed with a lower targeted SpO2 range will have less symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' corrected age (CA), whether they develop CLD or not.

Hypothesis #2- Relative to infants managed with prophylactic surfactant and conventional ventilation, infants who are managed with the early use of CPAP and a permissive ventilator strategy will have less symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' CA, whether they develop CLD or not.

Design

This study is a longitudinal follow-up of infants enrolled in the SUPPORT Trial to determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care in the first 18-22 months' CA.

Definition of outcomes:

A) Parental Report Symptomatic Airway Dysfunction Defined as Recurrent Wheezing or Chronic Cough
B) Parental Report of Physician Diagnosed Wheezing
C) Volume of Outpatient Pulmonary Care including number of pulmonary medications, office and emergency room visits and re-hospitalizations for respiratory illnesses.

Ascertainment of outcomes:

Outcomes will be measured at 4 time points in the first 18-22 months' CA as follows:

1. NICU discharge -baseline interview at to obtain family and environmental history
2. Six months' CA - telephone or face to face interview to ascertain incidence of symptomatic airway dysfunction and obtain interval history of need for pulmonary care.
3. Twelve months' CA - telephone or face to face interview as at 6 months'
4. 18-22 months' CA- Prior to or as part of the NICHD follow-up clinic visit, a telephone or face to face interview will be conducted to ascertain incidence of symptomatic airway dysfunction and obtain history of need for pulmonary care.

Anticipated Results

We anticipate that, for infants who develop CLD and those who do not, treatment with a lower vs. higher targeted oxygen saturation range will have less symptomatic airway dysfunction and less need for outpatient pulmonary care in the first 18-22 months' CA. We also anticipate that greater use of CPAP compared with conventional management will be associated with less symptomatic airway dysfunction.

Benefits and Risks

The proposed SUPPORT Breathing Outcomes Study will directly measure symptomatic airway dysfunction and outpatient pulmonary morbidity in infants treated with either a higher vs. lower targeted oxygen saturation. These data will provide important insight into the effect of different levels of supplemental oxygen exposure on airway growth and development in formerly premature infants. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the neurodevelopmental follow up visit. We anticipate no risk to patients enrolled in this observational follow-up study.

B. STATEMENT OF THE PROBLEM

Premature infants have a greater risk for recurrent wheezing, chronic cough and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor, the etiology of symptomatic airway dysfunction, defined hereafter as recurrent wheezing and/or chronic cough, in formerly premature infants is not known.

C. HYPOTHESES

The overarching hypothesis is that premature infants exposed to supplemental oxygen and, to a lesser extent, mechanical ventilation, in the immediate neonatal period suffer oxidant stress in the lung that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction, respiratory symptoms and need for pulmonary care when challenged with subsequent environmental or infectious exposures.

Specific Hypotheses:

Hypothesis #1- We hypothesize that relative to infants managed with a higher SpO2 range, infants managed with a lower SpO2 range will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care at 18-22 months' CA.

Hypothesis #2- We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

Hypothesis #3- We hypothesize that **among infants with CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

Hypothesis #4- We hypothesize that **among infants without CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

D. SPECIFIC AIMS

The goal of this project is to understand better the etiology of symptomatic airway dysfunction among formerly premature infants during early childhood by examining the interaction of oxygen exposure (targeted SpO2 range), surfactant therapy and early nasal CPAP in the newborn period.

SA#1 - Measure the effect of lower vs. higher targeted SpO2 on the incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care among infants born $24^{0/7}$ - $27^{6/7}$ weeks' gestation during the first 18-22 months' CA.

SA#2 - Measure the effect of early CPAP and permissive ventilator strategy compared with prophylactic surfactant and traditional ventilator strategy on the incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care among infants born 24-27 weeks' gestation during the first 18-22 months' CA.

SA#3 – Among infants who develop CLD, determine whether CLD is milder in infants managed with low compared with high targeted SpO2 by measuring incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

SA#4 – Among infants who do not develop CLD, determine whether pulmonary outcome is better for infants managed with a low compared with high targeted SpO2 range by measuring incidence of symptomatic airway dysfunction and need for outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

E. RATIONALE/JUSTIFICATION

Although synergy in producing airway injury may exist between oxygen toxicity and mechanical forces applied to the lung, animal and human data suggest that exposure to high concentrations of supplemental oxygen alone is sufficient to cause airway narrowing and greater airway dysfunction when exposed to subsequent environmental or infectious challenges. Understanding the relative contributions of oxygen toxicity and mechanical forces on airway growth and development may facilitate development of targeted therapies for preventing or reducing symptomatic airway dysfunction in premature infants.

Why measure symptomatic airway dysfunction and outpatient pulmonary care as an outcome from a clinical NICU interventional trial?

1) Important information will be available on the effect of oxidant gas exposure on airway development and later symptomatic airway dysfunction. Exposure to oxidant gas has been causally linked with later wheezing. Existing data on the relationship between supplemental oxygen therapy and wheezing come from longitudinal cohort studies, a design that suffers from intrinsic limitations that make controlling for potential confounders of respiratory outcome difficult. By randomizing infants to higher vs. lower target saturation ranges, and thereby presumably higher or lower concentrations of inspired oxygen, *the SUPPORT Trial creates a unique, and perhaps the only, opportunity to evaluate the effect of different levels of supplemental oxygen on subsequent symptomatic airway dysfunction and need for outpatient pulmonary care after NICU discharge.*
2) Using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care can be directly quantified, allowing assessment of whether infants both with and without CLD have improved pulmonary health as a result of the study intervention.
3) The incidence of CLD, defined as an oxygen requirement at 36 weeks' PMA, is an incomplete measure of pulmonary outcome in formerly premature infants during early infancy. CLD as defined above reflects alveolar gas diffusion and NICU oxygen needs. However, outpatient pulmonary morbidity for formerly premature infants is often airway related, involving wheezing either as a primary symptom such as bronchiolitis or as a complicating symptom of lower respiratory tract infection such as pneumonia. The studies proposed here will directly measure the effect of a randomized NICU-based clinical intervention on symptomatic airway dysfunction and outpatient pulmonary morbidity.
4) The risk of a negative trial is reduced. Because the diagnosis of CLD does not completely predict need for outpatient pulmonary care, clinically significant improvements in pulmonary morbidity may occur with minimal or no change in the incidence of CLD. This result has occurred in other interventional trials in which no difference in CLD were observed (12).
5) At present, there is no standard way to measure symptomatic airway dysfunction in premature infants in NICHD pulmonary intervention trials. There is need for a better measure to assess clinical pulmonary outcome to recognize and promote therapies that reduce need for outpatient care of former extremely premature infants.

F. BACKGROUND / PREVIOUS STUDIES

Recurrent Wheezing In Preterm Infants is a Significant Public Health Problem

Outpatient pulmonary morbidity, especially recurrent wheezing and need for outpatient pulmonary care, is an understudied but clinically important outcome measure for former premature infants with and without CLD. Infants born weighing < 1500 grams (very low birth weight, VLBW) and especially infants born weighing < 1000 grams are at increased risk for small airway narrowing, airway hyperreactivity, wheezing, and nighttime cough (1-11). Up to 30-40% of formerly extremely premature infants have episodes of wheezing after NICU discharge

with many requiring bronchodilators and frequent health care visits. Up to 40-50% of premature infants require re-hospitalization, mostly for treatment of respiratory illnesses (9;12;13). In analysis of cross sectional data from the National Maternal Infant Health Survey and 1991 Longitudinal Follow up Survey, the prevalence of asthma-like recurrent wheezing varied markedly with birth weight. Infants with normal birth weight (NBW, > 2500 grams) had a 6.7% prevalence of asthma compared to 10.9% of low birth weight infants (LBW, 1500-2499 grams) and 21.9% for VLBW (14). Mean per capita asthma related costs have been estimated to be 5 times greater for VLBW compared with NBW infants. The net effect is that VLBW infants, who comprise 2% of asthma patients, consume up to 7% of asthma-related therapy costs (14).

Animal Studies

Animal studies suggest that exposure of the premature lung to hyperoxia (without concomitant mechanical ventilation) for relatively brief periods is sufficient to cause airway remodeling and smooth muscle changes that predispose toward airway narrowing and hyperreactivity to subsequent environmental challenges (15-18). In a rhesus monkey model of asthma, Schlegle et al. exposed infant monkeys to repeated cycles of inhaled House Dust Mite Allergen (HDMA), ozone or filtered air. While repeated exposure to either ozone or HDMA had mild effects, exposure to cycles of ozone followed by HDMA resulted in asthma like changes with significant increases in serum IgE, serum histamine, peripheral eosinophilia and greater airway reactivity. Using supplemental oxygen rather than the stronger oxidant ozone, Schulman et al. found that exposure of newborn guinea pigs to 70% oxygen for 96 hours resulted in airway hyperreactivity at 2 and 9 days after the cessation of oxygen. In cell models, intracellular glutathione buffers airway cells against oxidant injury during hyperoxia (19;20). Although the critical period for lung development is comparatively brief in laboratory animals compared with human infants, the duration of hyperoxic exposure (and risk of oxygen toxicity) for treatment of neonatal lung disease may extend for much longer periods in premature infants known to be deficient in anti-oxidant systems such as intracellular glutathione.

Premature Infants <u>With CLD</u> Are At Greatest Risk For Airway Dysfunction

Among premature infants, infants with bronchopulmonary dysplasia (BPD) are at highest risk for poor pulmonary outcome after NICU discharge. Infants with CLD have small airway compromise with decreased forced expiratory flow velocities, airway hyperreactivity, and increased functional residual volume suggesting airway obstruction (2;5;9;21-24). In a pulmonary follow up of infants with RDS or BPD, De Klein et al. found infants with BPD had reduced FEV1 at baseline while infants with RDS but not BPD had significant improvements in FEV1 following bronchodilator therapy. In this study, a history of recurrent wheezing predicted abnormal pulmonary function (25). In a recent study of infants with CLD, Robin et al. found that 50% of infants with CLD had symptoms of recurrent wheezing and 35% showed significant airway responsiveness to bronchodilators, evidenced by a 24% increase in forced expiratory flow velocity at 75% of expired forced vital capacity (FEF_{75}). This study demonstrated the relationship between recurrent wheezing as a clinical symptom and the physiologic measurement of airway obstruction. Infants with CLD and a history of recurrent wheezing showed greater hyperinflation, expiratory flow limitation and airway responsiveness to albuterol compared to those without a history of recurrent wheezing (24).

Premature Infants <u>Without CLD</u> Have Significant Airway Dysfunction

Among VLBW infants who do not develop CLD, several studies of pulmonary outcome have found an association between neonatal oxygen exposure and increased prevalence of expiratory flow dysfunction and airway hyperreactivity (4;11;26-29). Some authors attribute reductions in airway function to intrinsically small airways as a consequence of poor intrauterine growth rather than superimposed airway injury or reactivity from neonatal respiratory disease (1;30). However, because small airways alone do not fully explain airway hyperreactivity, other mechanisms of small airway dysfunction are necessary to explain respiratory symptoms.

Several pulmonary outcome studies have reported significant increases (2-fold or more) in airway obstruction among VLBW infants without CLD following exposure to as little as 40% oxygen for 5 days (3;4;8;26). Not all studies have had similar results suggesting variability in effect or susceptibility of babies to oxygen exposure (31;32). In 1982, Coates et al. described increased small airway resistance at 10 year follow up of mildly

premature infants (mean gestational age 31 weeks and birth weight 2000 grams) treated with a high oxygen regimen and those exposed to a low oxygen regimen for the treatment of respiratory distress syndrome (RDS). Mechanical ventilation was not used in either group. Pulmonary function tests were performed on survivors receiving either the low or high supplemental oxygen regimen ten years after their initial illness. Infants treated with high levels of supplemental oxygen alone (no mechanical ventilation) had decrements in airway function similar to decrements in function reported for a historical cohort of RDS survivors treated with ventilation and high levels of supplemental oxygen. From these data, the authors concluded that neonatal exposure to high oxygen concentrations in the absence of mechanical ventilation is capable of causing long-term change in small airways (28). These studies suggest that use of lower supplemental oxygen concentration may improve respiratory health of infants who do not develop CLD.

Premature Infants Without CLD Have Increased Risk of Symptomatic Airway Dysfunction and Need for Outpatient Pulmonary Care.

For VLBW infants without CLD, the prevalence of parental or physician reported wheezing is increased compared with term infants, with estimates of the prevalence of wheezing ranging from 10-38% (4;8). Prevalence of wheezing requiring medications is greater compared with term infants. VLBW infants have a 2-4-fold increase in respiratory related re-hospitalization rates compared with term infants (4;8;33-35). Although most studies have found the risk of recurrent wheezing remains elevated throughout childhood, an Australian longitudinal follow-up cohort of VLBW infants found the prevalence of wheezing remained elevated for 2 years then returned to baseline (32;36).

Prevalence of Symptomatic Airway Dysfunction in Formerly Preterm Infants During the Surfactant Era Remains High

With the advent of surfactant therapy, survival of small infants increased dramatically and the incidence of CLD changed minimally (37-40). Classic BPD evolved into the "new CLD" characterized by reduced alveolarization and more variable airway changes (41). Pulmonary follow up studies during the surfactant era showed reduced pulmonary morbidity in surfactant treated patients. Typical of these studies, Sell et al. found the incidence of asthma was significantly lower in infants given synthetic surfactant compared with those given air placebo. Pelkonen et al. performed PFT measurements on 40 children aged 7-12 years who were born before 30 weeks of gestation with an immature surfactant system, and were randomized to one of three treatment groups: prophylactic surfactant, rescue surfactant and placebo (air). Spirometric parameters of children born preterm were compared with those of 20 children born at term. Bronchial obstruction was found in 53% of the prophylactically treated group, in 36% of the rescue group, in 67% of the placebo group, and in 0% of the control group (42). A recent report suggests that the introduction of surfactant therapy markedly altered the pulmonary outcome of premature infants. Published in 2001, the Newborn Lung Project Group reported results of a prospective 12-year follow-up of VLBW infants following the introduction of surfactant therapy (5;8;43). Among infants with CLD, wheezing symptoms decreased from 50 to 16% from the period before compared with the period after surfactant therapy became available. However, among infants without CLD the prevalence of wheezing increased from 14% to 38% with the introduction of surfactant. These data suggest that surfactant therapy has an effect on outpatient respiratory health and underscores the need to consider outpatient pulmonary outcomes in evaluating therapeutic strategies that potentially decrease surfactant replacement therapy.

CLD is an Incomplete Predictor of Outpatient Pulmonary Morbidity

Several authors have looked to respiratory symptoms and need for outpatient pulmonary care as outcome measures for neonatal lung disease (9;10;12;24). In 1988, from a retrospective chart review of 605 premature infants < 1500 grams, Shennan et al. found that the presence of BPD (oxygen requirement at 36 weeks PMA) had a 63% positive predictive value and a 90% negative predictive value for abnormal pulmonary outcome in the first 2 years of age. However, this study from before the era of exogenous surfactant therapy defined abnormal pulmonary outcome as death, oxygen requirement at 40 weeks PMA, 2 or more respiratory related hospital admissions, wheezing requiring drug therapy or persistent wheezing resulting in growth failure, handicap or hypotonia at 1 year of age. Such restrictive criteria for abnormal pulmonary outcome are likely to underestimate the burden of recurrent wheezing on former premature infants and their families. Several recent

interventional studies show that CLD is an incomplete predictor of clinical wheezing and need for outpatient pulmonary care and suggest that differences in oxygen exposure or oxidant stress may affect pulmonary outcome without affecting the incidence of CLD.

Interventional Trials That Did Not Reduce CLD But Did Reduce Outpatient Pulmonary Morbidity.

Recent data in preterm infants treated with human recombinant superoxide dismutase (SOD) found that anti-oxidant therapy did not reduce the incidence of CLD. However, among infants < 27 weeks gestation, SOD therapy resulted in significant reductions in the first year after NICU discharge in the number of emergency room visits and number of re-hospitalizations for respiratory problems and reductions in the need for bronchodilators suggesting a reduced prevalence of wheezing in patients treated with SOD (12). In a randomized, multi-center trial from Helsinki, N acetyl cysteine did not reduce the incidence of CLD. Outpatient pulmonary outcome of these patients has not been reported.

Treatment of Premature Infants With Higher Targeted Oxygen Saturations Is Associated with Poorer Pulmonary Outcome

In the STOP-ROP Study, infants exposed to higher levels of oxygen to achieve a targeted saturation of 96-99% compared with 89-94% had greater risk of adverse pulmonary events including pneumonia, chronic lung disease exacerbations and need for diuretics, oxygen and hospitalization at 3 months' corrected age. *Although all infants in this study had CLD at enrollment, different targeted oxygen saturations were associated with large differences in pulmonary morbidity.* Adverse pulmonary outcomes occurred with differences in FIO2 of as little as 10% for patients treated with ventilation, CPAP or hood (36% $\pm$ 14% vs. 46% $\pm$ 20%, respectively for low vs. high saturation range) and 5% for infants treated with nasal cannula, (26% $\pm$ 6% vs. 31% $\pm$ 11%, respectively for low vs. high saturation range) (44). In a similar study, The Benefits of Oxygen Saturation Targeting (BOOST) Trial randomized infants < 30 weeks' gestation to higher (95-98%) or lower (91-94%) saturations ranges beginning at 32 weeks' PMA to determine whether infants managed with higher targeted saturation range showed better growth and neurodevelopment. As in the STOP-ROP study, need for oxygen therapy was prolonged. Trends towards an increased risk of pulmonary death and fewer outpatient office visits (median 27.5 vs. 31.3, $p < .11$) were seen in the lower targeted oxygen saturation group (13).

Factors In Addition To Prematurity and Oxygen Contribute To Symptomatic Airway Dysfunction

Multiple factors in addition to prematurity and oxygen contribute to the development of airway dysfunction in children (Table 1). In the SUPPORT TRIAL Breathing Outcomes Study, these potential covariates will be measured and controlled for using a randomized trial design. These covariates will also be evaluated as independent predictors of pulmonary outcome in multivariate analyses.

Table 1. ***Important Covariates in Etiology of Recurrent Wheezing***

Demographcis – race, sex, ethnicity, parental factors (educational level, poverty status, and age), and family history of wheezing or atopy.

Environmental – daycare, siblings, crowding, tobacco smoke or wood smoke in the home, pets

Health Services – health care and respiratory medication use appropriate for level of respiratory symptoms

Medical- congenital anatomic airway abnormalities, neonatal sepsis, RSV and other viral infections

G. METHOD/ PROCEDURES

NICHD SUPPORT Trial Breathing Outcomes Study

G.1 Description of study design

This study will add an 18-22 month longitudinal, prospective follow-up study of surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial.

G.2 Definition of study population

Infants with gestational age of $24^{0/7}$-$27^{6/7}$ weeks' gestation by best obstetrical estimate.

Inclusion criteria:

- Enrollment in the SUPPORT Trial
- Survival to hospital discharge
- Consent for enrollment into the Breathing Outcomes Study, obtained either at the time of enrollment into the SUPPORT Trial or separately.

Exclusion criteria

- Refusal of informed consent

G.3 Description of study intervention

Before delivery, infants will be randomized to subsequent management with high vs. low target oxygen saturation according to the SUPPORT Protocol. The SUPPORT Breathing Outcomes Study begins just prior to NICU discharge (Figure 1).

Figure 1.

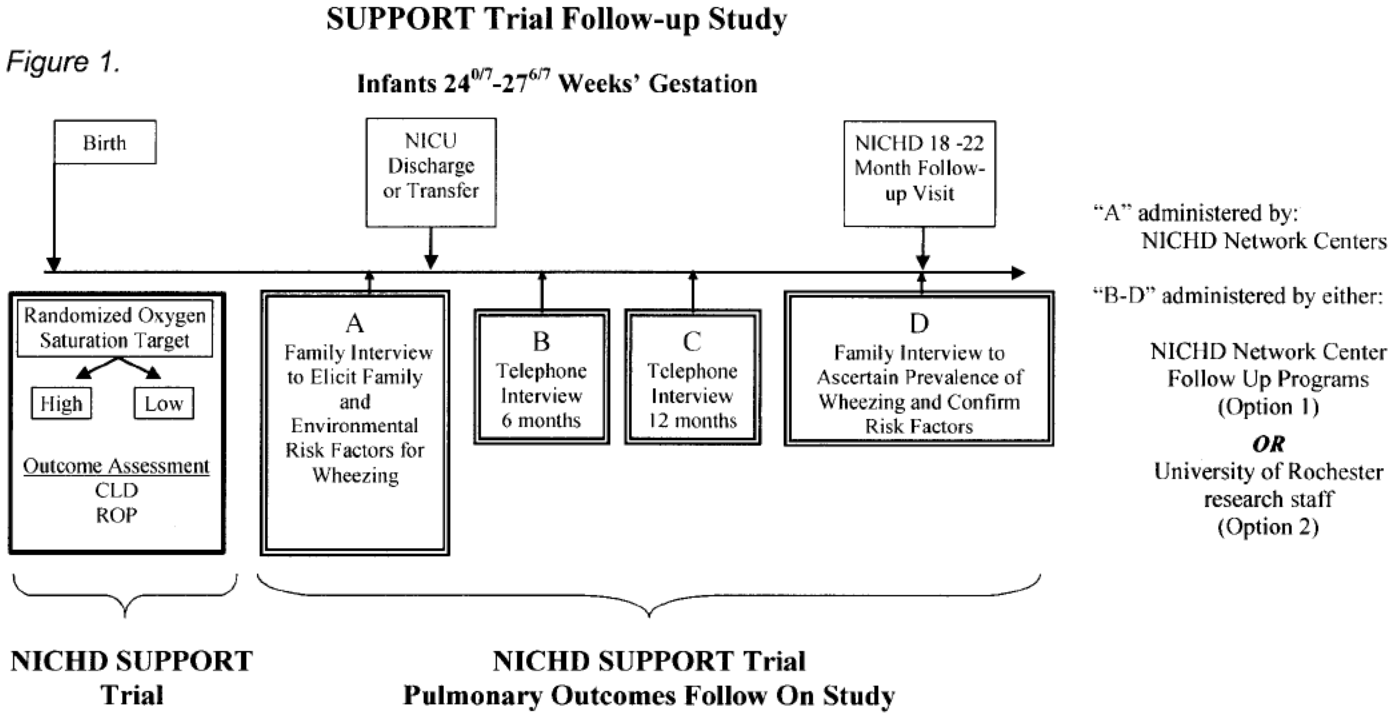

Fig 1, A. Parent (Guardian) Interview to Elicit Family and Environmental Risk Factors for Wheezing and Cough The family interview will be administered either face to face or by telephone to study

participants by site study staff prior to or within 30 days of NICU discharge. The questions are based on intake questions used by the Tucson Respiratory Study and are designed to elicit family history of asthma, atopy, and home environmental exposures and to identify likely care givers (NICU Discharge – Baseline Interview).

Fig 1, B. *Interview at 6 months PMA* – respiratory interval history

Fig 1, C. *Interview at 12 months PMA* – respiratory interval history

Interviews will be undertaken at 6 and 12 months to obtain an interval history of respiratory problems including wheezing, cough, medications used, and health services sought for respiratory related problems (6 and 12 Month Questionnaire). Interviews may be administered either by telephone or face to face.

Fig 1, D. *Parental Interview to Ascertain Incidence of Wheezing and Cough and Confirm Risk Factors*

This parent interview may also be administered either by telephone prior to the regularly scheduled 18-22 month NICHD developmental follow up clinic visit or face to face at the time of the visit. Contacting parents prior to the office visit will help improve the Developmental Follow Up Clinic attendance rate and will allow the clinic visit to provide a back up means to contact the family. The 6, 12 and 18-22 month interviews will be conducted either by the local NICHD Follow Up Program (Option 1) or long distance from Rochester (Option 2), based on center preference (see table 2 below). The interview questionnaires are based on questionnaires administered by the Tucson Respiratory Study at approximately one year of age (18-22 Month Questionnaire). Questions are designed to ascertain the frequency and severity of wheezing and cough episodes and to assess need for outpatient pulmonary care. In addition, risk factors obtained at the 1st interview will be confirmed.

Each interview will collect a 6 month interval history, which, when taken together, will provide a complete respiratory history over the first 18-22 months' corrected age. If one questionnaire is not completed, the subsequent questionnaire will include the full interval history since the last completed questionnaire.

To standardize administration of the interview, the Rochester site will lead an interviewer training program consisting of two parts. Part 1 will consist of a teleconference to discuss study questions and interview script in question by question detail. Part 2 will consist of a practice interview in which interviewers from each center interview the Rochester trainer, who simulates a standardized patient. Following the practice interview, the Rochester trainer and practice interviewer will discuss the interview and give feedback. All interviewers will be required to complete this training.

Table 2. **SUPPORT Trial - Breathing Outcomes Study**

NICHD Site	*6, 12 and 18-22 Month Pulmonary Questionnaires Administered By*	*Option Number*
Alabama	Alabama	1
Brown	Brown	1
Cincinnati	Cincinnati	1
CWRU	CWRU	1
Dallas	Dallas	1
Duke	Duke	1
Emory	Rochester	2
Houston	Rochester	2
Indiana	Rochester	2
Miami	Miami	1
Rochester	Rochester	2
Stanford	Rochester	2
UCSD	UCSD	1
Wake Forest	Wake Forest	1
Wayne State	Wayne State	1
Yale	Yale	1

G.4 Precise definition of co primary/secondary outcomes

G.4.1 Definition of primary outcomes- parental report of recurrent wheezing and chronic cough.

Two primary outcomes will be measured, the incidence of recurrent wheezing and incidence of chronic cough. Whether individual symptoms (recurrent wheezing or chronic cough, alone) or a combination of these symptoms (wheezing and/or chronic cough, together) best quantifies symptomatic airway dysfunction following premature birth is controversial. Many studies have used wheezing alone as a primary outcome measuring pulmonary morbidity in formerly premature infants (10;12;14;48). In 1996, Greenough, using a combined outcome of either wheezing or chronic cough as a measure of symptomatic airway dysfunction, found that greater pulmonary symptoms were associated with longer durations of supplemental oxygen and mechanical ventilation (49;50). Later, in a follow-up study of infants enrolled in The United Kingdom Oscillator Study (UKOS), Greenough found that frequent wheezing episodes but not chronic cough were associated with neonatal respiratory events (51;52). In our study, to address this issue most conservatively, recurrent wheezing and chronic cough will be measured as co-primary outcomes. Secondary analyses will consider these outcomes in combination.

The incidence of wheezing will be ascertained using the primary question used and validated in the Tucson Children's Respiratory Study (a large prospective birth cohort study of term infants) (53-59), "Has his/her chest ever sounded wheezy or whistling?" (53). Likewise, the incidence of cough will be ascertained using the Tucson question, "Has this child ever had a cough when he/she did not have a cold?" (53). As in Greenough's study, recurrent wheezing will be defined as episodes of wheezing occurring more than twice/week. Chronic cough will be defined similarly, cough occurring as more than twice/week. Additional questions will further characterize the wheezing and coughing episodes, including whether symptoms were associated with a viral illness (parental report of a "cold") or an environmental exposure. A symptom diary will be offered to study participants to help facilitate recall of pulmonary symptoms and need for outpatient pulmonary care.

The Tucson Children's Respiratory Study administered the questionnaires both in person and by phone, depending on patient availability. The investigators did not undertake a formal validation of phone vs. face-to-face administration of the questionnaire. Anecdotally, based on phone conversation with the study coordinator, investigators did not observe a difference in quality of responses between phone and questionnaires administered in person.

G.4.1.1 Standard Definition of Wheezing

Several studies have found that multiple colloquialisms in both English and Spanish can be used to describe wheezing (60-64), creating opportunity for misinterpretation of respiratory sounds and potential for over or under estimation of the incidence of wheezing. Other studies have found that clips of respiratory sounds played for families improve accuracy of symptom reporting (65;66), providing data relatively free from biases due to language, culture, literacy or interviewing techniques. To minimize misinterpretation of other respiratory sounds as wheezing, we will provide a verbal AND a brief audio clip that can be played for the interviewee at the beginning of the interview (electronic clip included separately). Accompanying the audio clip, wheezing will be defined verbally by the interviewer as an expiratory sound (a sound that is made when breathing out, not in) coming from the chest, sometimes described as whistling or musical. Although not yet widely used, use of audio clips to standard symptom definition is the best approach to bridge the language gap that exists between English and Spanish and among Spanish speaking populations using different dialects or colloquialisms.

In administering the questionnaires, every effort will be made to accurately measure the occurrence of pulmonary symptoms and health care and medication use, thus establishing the true incidence of pulmonary morbidity in the study population as a whole. Most importantly, however, because pulmonary morbidity is a blinded outcome of a randomized controlled trial, bias favoring one study arm over another should not occur.

G.4.1.2 *Parental Report for Non-English Speaking Populations*

Upon finalization of the questionnaires, Spanish language versions will be created and made available to all centers. The Cornell Translation Service, a University based professional translation service, will be contracted to perform the translation. For centers choosing to administer the questionnaires locally (Option 1), each center will be free to choose their primary interviewer who has the necessary skills. Administration of the questionnaire by a native speaker of the local Spanish dialect is recommended. For centers choosing Rochester to administer the questionnaire to their patients (Option 2), English and Spanish speaking individuals, trained to administer the questionnaires, will conduct the telephone or face to face interviews. An audio clip and verbal definition of wheezing will be presented to the respondent to standardize interpretation of wheezing and to minimize ascertainment biases due to language, culture, literacy or interviewing techniques.

G.4.1.3 *Parental Report of Pulmonary Symptoms Is a Reliable Outcome Measure of Airway Dysfunction*

Evaluation of frequency and severity of respiratory symptoms by parental questionnaire and need for pulmonary care has been used as the primary outcome in multiple follow up studies of term and premature infants (10;12;14;48). A recent review evaluated the value of respiratory symptom history ascertained by parental questionnaire in determining the risk for developing asthma in early childhood. By evaluating 9 large, longitudinal, full term birth cohort studies and reviewing the original questionnaire from 7 of these studies, Koopman found that the questions posed to parents eliciting a history of wheezing in their infants were similar. Parental report of wheezing predicted an increased risk for later respiratory symptoms, including asthma. In the studies proposed here, incidence of recurrent wheezing and chronic cough ascertained by parental report will be primary outcomes, rather than physiologic measurements of airway dysfunction, for several reasons.

G.4.1.4 *Reasons to Use Parental Report of Recurrent Wheezing and Chronic Cough as Primary Outcomes*

- Parental interview can be performed more readily on large numbers of patients. The validity of this approach has been shown in several longitudinal studies including The Tucson Respiratory Study.
- Recurrent wheezing is highly correlated with changes on pulmonary function testing (PFT). In infants with CLD, a history of wheezing was associated with greater expiratory flow limitation, hyperinflation and airway responsiveness to albuterol on PFT compared to those without such a history (24).
- Parental recall of respiratory illnesses has been shown to correlate strongly with review of medical office records. For asthma and bronchitis in the past year, Pless et al. found good agreement between recall of 288 parents and physician office chart review. Parental education and occupation were not predictive of a parent's ability to recall the illness (67). In an assessment of parental recall done to evaluate minor injury in children, Harel found recall declined with time, with the best recall occurring in the first 3 months after injury with further decline after 6 months from the time of the injury (47;68;69).
- Symptomatic airway dysfunction can be assessed in a standardized way. The NHLBI Consensus Expert Report developed standardized questions to assess severity of airway dysfunction. Three standardized questions from this report will be administered at 6, 12 and 18 months to assess symptom severity (70).

G.4.2 Definition Of Secondary Outcomes - Physician Diagnosed Wheezing. A secondary outcome will be parental report of physician diagnosed wheezing, defined as an episode of wheezing occurring at a health care visit. Physician diagnosed wheezing will be collected by parental report during the telephone or face to face interviews, using the question "Has your child been diagnosed with wheezing by a doctor?"

G.4.3 Definitions of Secondary Outcomes - Measures Need and Volume of Outpatient Pulmonary Care
Important secondary outcomes of outpatient pulmonary morbidity will be collected (Table 3).

Table 3. *Secondary Outcomes, Covariates and Sources*	
Outcomes	Source
Secondary Outcomes	
Number and duration of outpatient pulmonary medications including bronchodilator, diuretic, methylxanthine, and inhaled and systemic steroid therapy.	Family interview
Number of office visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview
Number of emergency room visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview
Number of re-hospitalizations for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview
Growth at 18 months PMA (height, weight and head circumference)	NICHD follow up clinic data

G.4.4 Data Collection

Data collection for The Breathing Outcomes Study will be accomplished using one of two options (Figure 2, Table 2). Regardless of Option chosen, each local center will be responsible for obtaining informed consent and tracking patients following discharge.

Consent: For both options, every effort will be taken to enroll ALL SUPPORT patients into the Breathing Outcomes Study, including currently enrolled SUPPORT patients (both patients still in NICU and those discharged) and future enrollees. By obtaining pulmonary outcome data for both current and future SUPPORT patients, death or adverse pulmonary outcome can be analyzed as competing outcomes. Sample consent forms for currently enrolled and future SUPPORT patients are attached.

Figure 2.	Option 1	Option 2	
	Local Center	Local Center	Rochester
Consent / IRB	✓	✓	
Questionnaire at Discharge	✓	✓	
Patient Tracking	✓	✓	
Questionnaire at 6 & 12 mo.	✓		✓
Questionnaire at 18-22 mo.	✓		✓
Data Entry (questionnaires)	✓		✓

G.4.4.1 Data Collection: Ascertainment of Outcomes - Field Work

A. Ascertainment of Wheezing and Outpatient Pulmonary Morbidity By Interview.

There will be 4 parental interviews over 18-22 months, one face to face interview or telephone prior to or within 30 days of NICU discharge and 3 subsequent interviews (by telephone or face to face) at 6 month intervals to collect data on recurrent wheezing, chronic cough and volume of outpatient pulmonary care (Figure 1, A-D above). Based on review of longitudinal studies of full term infants in which follow up patient contacts occurred quarterly to once every 18 months', a 6 month interval for follow up patient contacts is planned in an effort to reduce parental recall omissions which are more likely to occur with less frequent follow up (48;68). The 4 interviews are designed to collect the primary and secondary outcomes of the follow-up study. Other inpatient and outpatient data will be collected as part of the NICHD Neonatal Network Generic Database (GDB) and Follow-up Program.

B. Interview Instruments – Questionnaires are based on the Tucson Children's Respiratory Study, a longitudinal cohort study that followed healthy term infants from birth to over 20 years of age. Questionnaires have been updated with validated symptom severity and tobacco smoke exposure questions, a current list of available respiratory medications and modifications that address health issues faced by formerly premature infants such as use of palivizumab for RSV prophylaxis. The original Tucson questionnaires are designed to elicit a thorough history of possible covariates, such as environmental and infectious exposures and family histories of atopy, asthma or respiratory disease.

C. Administration of Interview Instruments – Six, 12 and 18-22 month interviews will be initiated in one of two ways (table 2):

C.1 Option 1 - NICHD Network Center Follow Up Programs (local contact)

Individual NICHD Network Centers may choose to undertake administration and tracking of patients enrolled in the SUPPORT Breathing Outcomes Study. Local administration of the questionnaires capitalizes on existing NICHD resources available at local centers. Each Network Center choosing local administration of the telephone or face to face questionnaire will identify one or more interviewers who will undergo training in the administration of the questionnaire and tracking of enrolled patients. The Rochester Health Service Research Group will provide training and server as a resource to answer questions regarding administration of the questionnaire (outlined above).

Advantages of Conducting Telephone Interviews From the Local Network Centers

Conducting the telephone interviews from Local Centers will:
1) reduce risk for HIPPA violation
2) capitalize on existing rapport between the patient's family and their local center
3) avoid redundancy in making tracking calls to families

C.2 Option 2 - University of Rochester research staff (long distance contact)

The University of Rochester Neonatology Research Group has conducted similar telephone interview designs as part of an ophthalmologic outcome study of patients enrolled in a randomized trial of cryotherapy to treat ROP and a 15-year, longitudinal neurological assessment conducted by telephone survey among 132 infants treated with surfactant. Telephone follow up rates were 96% follow up at 7 years and 95% follow up at 15 years (71). In the study proposed here, the University of Rochester Health Services Research Group (HSR Group), will conduct the telephone interviews.

In telephone follow up surveys conducted by the HSR Group, follow up rates at 12 months' have exceed 75% in populations at high risk for being lost to follow up (72-78). Working with NICHD Network Centers to assist in tracking local families, follow up rates for this Follow-up Study are expected to exceed 80% and should approach the average annual NICHD follow up rate of 83%.

To facilitate tracking and record keeping, Network Centers choosing Rochester to administer questionnaires to their patients (table 2) will provide contract information to the Rochester site. RTI International will provide monthly updates of patients due for interviews. Local centers will be responsible to maintain updated contact information. Each interview will close with a question as to whether the family plans a new address or phone number prior to the next interview. The names and phone number of a friend or relative will be sought so that they may be contacted in the event that contact with the patient is lost. If contact information is updated, the new contact information will be transmitted back to the local center. By interviewing families every 6 months, a higher follow up rate will be achieved because family contact information will not become so out of date that the family is lost or that re-contacting them is inefficient. We anticipate that each interview will require 2 hours of staff time, with 20-30 minutes to conduct the interview and 90 minutes to contact family and enter data.

Advantages of Conducting Telephone Interviews From a Central Research Facility

Conducting the telephone interviews from Rochester will:
1) require less effort from the individual Network Centers
2) allow standardization of the telephone interview by a core group of trained interviewers
3) blind the telephone interviewer to the SUPPORT Trial study group designation
4) reduce the cost of the study by consolidating the telephone training and follow up at one site.

G.4.4.2 Data Collection: Ascertainment of Environmental and Genetic Covariates

Ascertainment of important environmental exposures and genetic risk factors that might confound the relationship between supplemental oxygen exposure and symptomatic airway dysfunction will be obtained along with the primary outcomes during the same interviews (Table 4). Tobacco smoke exposure is a potentially significant risk factor for airway dysfunction. The tobacco smoke question in the Tucson Study has been replaced by a question shown by Dr. Wakefield et al to correlate with cotinine levels in infants (79;80).

Table 4. Postnatal and Genetic Covariates Evaluated as Potential Confounders of Oxygen and Wheezing

Covariates in Home Environment and Exposures The initial questionnaire and 6 month interviews will gather information on other *inhaled exposures* (tobacco, wood stoves, cold air), *residence* (crowding, siblings, daycare), *infectious exposures* (RSV, palivizumab) and medical risk factors (congenital anatomic airway abnormalities)

Covariates in Family History Questionnaires will elicit *family history* of atopy (family history of asthma, eczema or allergy to foods, pets).

G.4.4.3 Data Collection: Ascertainment of Primary Exposure

Oxygen Exposure

In the SUPPORT Trial, it is assumed that managing infants with a higher vs. lower targeted oxygen saturation range will result in different levels of supplemental oxygen exposure. The SUPPORT Trial will collect data on FIO2 exposure to quantify the anticipated difference. As part of the SUPPORT Trial, FIO2 values will be recorded and analyzed at many time points including time of admission, first blood gas, and as described in the SUPPORT Manual of Operations, Chapter 10 Safety Monitoring Form. Because oxygen is the primary exposure in the SUPPORT Breathing Oucomes Study and plays a central role in the disease model proposed, oxygen exposure will be quantified as described in the main SUPPORT trial and analyzed as a predictor of later symptomatic airway dysfunction.

G.5 Sample size estimate with some statistical support based upon primary outcome

G.5.1 Sample Size

The SUPPORT Trial anticipates enrollment of 1310 patients $\geq 24^{0/7}$ and $\leq 27^{6/7}$ weeks' gestation, providing 80% power to detect a 10% difference between treatment groups in the incidence of death/CLD and death/stage III Retinopathy of Prematurity (ROP). Assuming mortality of 22% for infants in this GA range (NICHD 2001-2002 data), 1021 infants would be expected to survive and be eligible for the SUPPORT Breathing Outcomes study.

Power for detecting a difference between the high vs. low saturation groups for the primary outcome

First we consider power for detecting a difference between the high and low saturation groups for the first primary outcome, recurrent wheezing. We expect the incidence of wheezing to be about 0.17 in the low saturation group and about 0.31 in the high saturation group (12). For the power calculations, we also consider a scenario with a smaller difference between groups: 0.19 for the low saturation group and 0.29 for the high saturation group. We expect the follow up rate to be about 80% (NICHD historical average follow up rate), which would result in data on about 816 patients. We also consider a lower follow up rate of 65%, which would result in about 663 patients. Power to detect a difference between groups based on a chi-square test with type I error alpha set at 0.05 is given in Table 5 for each scenario. From those results, we expect to have more than 80% power for the primary outcome. Also of interest are subgroup analyses, where we look separately at the CLD and non-CLD subjects. Of survivors, we expect 37% or 378 infants to have CLD. For the CLD group, we expect the incidence of wheezing to be about 0.5 in the high saturation group and 0.3 in the low saturation group. If there is a 80% follow up rate, we will have 95% power to detect a difference between the two groups. For the non-CLD subgroup, we expect the incidence to be 0.2 and 0.1 in the high and low groups, respectively. With 80% follow up, we will have 92% power. Thus, we expect to have adequate power for the primary outcome even in the analyses stratified by CLD.

Table 5. Power for primary outcome.

Follow-up rate	Low Saturation	High Saturation	power
80%	0.17	0.31	0.99
80%	0.19	0.29	0.90
65%	0.17	0.31	0.98
65%	0.19	0.29	0.83

Power for detecting a difference between the high vs. low saturation groups for secondary outcomes

We expect the study to be adequately powered for analysis of important secondary outcomes such as use of pulmonary medications. Based on results reported in Davis et al. for infants less than 27 weeks' gestational age [22], we expect the rate of pulmonary medication use to be 0.42 in the high saturation group and 0.19 in the lower saturation group. In that case, even with a 65% follow up rate, we would have more than 99% power to detect a difference between the groups with a chi-square test. Similarly, the CLD subgroup analyses would have more than 80% power under those assumptions. Based on the power numbers above, we could potentially enroll fewer subjects in the trial and still have adequate power. However, we choose to over enroll slightly to make up for the fact that some patients will likely be lost to follow up. The recruitment time will be that of the SUPPORT Trial (2 years) with a run out period of 18-22 months to ascertain follow-up outcomes. The total study period is 36-40 months.

G.5.2 Data Analysis

Analysis of primary dichotomous outcomes will be performed by chi square test and presented as a relative risk for development of that outcome. Number of outpatient pulmonary visits for respiratory illnesses will be presented as median values. The Wilcoxon Rank Sum test, a non-parametric alternative to the two-sample t-test, will be used to test for differences between the two groups. Statistical analyses will need to consider the effect of multiple comparison groups on the level of statistical significance. All analyses will be performed in conjunction with the Research Triangle Institute (RTI, North Carolina). Data will be presented as shown in tables 6-7. Mean FIO2 values in the high and low SpO2 groups will be compared by two sample t-test. Analyses will be done to evaluate the effect of ventilator strategy on pulmonary outcome and presented similarly to table 6 and 7. Other secondary analyses will be performed, including analyses of respiratory outcomes by presence or absence of CLD (oxygen at 36 weeks' PMA determined by SUPPORT study criteria). The incidence of outpatient respiratory diagnoses, such as asthma or reactive airway disease, will be compared between intervention groups and, in sub group analyses, between intervention groups by presence or absence of CLD.

Table 6. *Primary Dichotomous Outcomes*	**Low Saturation**	**High Saturation**	**RR**	**CI**	**p-value**
Parental Report of Recurrent Wheezing (%)					
Parental Report of Chronic Cough (%)					
Need for Outpatient Pulmonary Medications (%)					
Need for Physician Visit for Respiratory Illness (%)					
Need for Re-hospitalization for Respiratory Illness (%)					

Table 7. *Primary Outcomes – Continuous Outcomes*	**Low Saturation**	**High Saturation**	**p-value**
Number of Physician Visit for Respiratory Illness (Median)			
Number of Emergency Visits for Respiratory Illness (Median)			
Number of Re-hospitalization for Respiratory Illness (Median)			

G.5.2 Expected Results

We predict that premature infants managed with a lower targeted oxygen saturation range compared to those managed with a higher targeted oxygen saturation are exposed to lower levels of supplemental oxygen and have reduced risk of recurrent wheezing in the first 18-22 months' CA.

G.5.2 Anticipated Problems and Solutions

1) Participant attrition. As seen in the sample size calculation, the potential for patients to be lost to follow up over time will be offset by over enrolling patients to participate in the follow up. Because patients who enroll in the SUPPORT Trial are randomized, there should be no systematic bias favoring one group over another among patients who are lost to follow up. However, if loss to follow up is in part caused by the treatment or outcomes, this could bias the results. We will therefore investigate whether there are differences in key variables for subjects who are lost to follow up compared to those who remain in the study. For example, we will test whether subjects in one treatment arm were more likely to be lost to follow up than in the other arm. Similarly, we will compare wheezing rates at 6 months' for those who are later lost to follow up compared to those who remain in the study. We do not expect to see any major differences.

2) Difficulty tracking families. With mobile families, keeping contact information up to date may be difficult. To promote successful follow up in both the Breathing Outcome Study described here and the routine NICHD neurodevelopmental follow up visit at 18 - 22 months, each center will be responsible to track families to maintain current contact information for both the family and primary care physician.

3) Center variability in administering the questionnaire. With 11 centers administering the questionnaires, variation in techniques and styles in administering the questionnaires has the potential to introduce ascertainment bias. To minimize this risk, staff administering the questionnaires will undergo an interviewer training program conducted by the Rochester Site. The program will consist of a conference call and a practice interview of a standardized patient.

4) The SUPPORT Breathing Outcomes Study has been prepared as the central project for Dr. Stevens' Patient Oriented Clinical Research Grant (K23 Award), revised submission 7/1/05. If approved, funds from the K23 will be available to offset a portion of the cost of conducting this Follow-up Study. If not approved, NICHD funding has been approved to support the project.

5) Initiation of the Breathing Outcomes Study after enrollment into SPPORT has begun.

5.1 Babies already enrolled in SUPPORT

To help assure pulmonary outcome assessment for all SUPPORT patients, families of babies already enrolled in SUPPORT will be approached with a separate consent to enroll in the Breathing Outcomes Study. IRB approval of this consent form will be required.

5.2 *Future babies eligible for enrollment in SUPPORT*

Going forward, a modified SUPPORT Consent Form, which includes consent for the Breathing Outcomes Study, will be need to be prepared at each center. **The revised SUPPORT Consent will require**

G.6 Available population/compatibility with other ongoing protocols

Another secondary study proposed by a group independent from ours is looking at the genetics of reactive airways disease in patients enrolled in the SUPPORT Trial. The follow on study proposed here should be complementary to the genetics study, enhancing the both the quality and quantity of data on the prevalence of wheezing and need for outpatient pulmonary care in patients enrolled in the SUPPORT Trial.

G.7 Estimate of projected recruitment time

The recruitment time will be that of the SUPPORT Trial with a 18-22 month period of follow up to ascertain primary and secondary outcomes.

H. RISKS / BENEFITS, WITH ESTIMATE OF FREQUENCY / SEVERITY OF RISKS.

By using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care may be quantified, allowing assessment of whether infants who develop CLD and those who do not have improved pulmonary health as a result of the study intervention. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the follow up visit. We anticipate no risk to the patient of this observational follow on study.

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NICHD SUPPORT Trial
Breathing Outcomes Study

NICU Discharge-Baseline Interview

This interview should be administered by trained study staff to the parent/guardian. The target window for this interview is prior to NICU discharge or within the first 30 days following NICU discharge. For patients enrolled in the Pulmonary Outcomes Follow up Study after this target window, this interview should be performed at the time of enrollment.

This interview is for:

_____
(Child's name)

All questions pertain only to his/her health.

N.B. Parents or guardians expressing concerns regarding their child's breathing should be advised to discuss them with the family's primary care physician.

Introduction to the Study:
Premature babies are more likely than full term babies to have breathing problems after discharge from the NICU. The purpose of this study is to see whether or not the treatment your baby received as part of the SUPPORT Study improves your baby's breathing in the 18-22 months following the baby's due date.

As part of this study, we will contact you every 6 months or so to ask you questions about your baby's breathing. The questions will be about your baby's breathing symptoms, especially wheezing and coughing, and about your baby's need for medical visits and treatments for breathing problems.

Wheezing can mean different sounds to different people. By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical.

We have prepared a brochure for you that describes the study and outlines important characteristics of your baby's breathing, especially breathing problems and treatments.

Give brochure

When we call, we'd like you to gather any notes, medications or other information about your baby's breathing. We will ask questions about how often your baby has wheezing or coughing, whether your baby visited a doctor's office, emergency room or was hospitalized for breathing problems, and whether your baby has needed breathing medicines or treatments. If you wish, you may use the brochure to make notes about your baby's breathing.

In order to help us understand your baby's breathing and risk for breathing problems at home, we'd like to ask you a few questions about your home and about whether breathing problems run in the family. As with all information we collect, the answers to these questions will be kept confidential.

NICU Network	SUPPORT TRIAL Breathing Outcomes Study	SUPF01 Rel 1.0 October 12, 2005

NICU Discharge-Baseline Interview

Center: ___ Site: ___ Network No. _____ SUPPORT Follow-up No. _____ Birth No. ___ Mother's Initials: ____

1. Child's Name_____ _____ (first) (last) 2.Today's Date: |__|__| - |__|__| - |__|__|__|__| mm dd yyyy

3. Child's Sex: 1~ Male 2~ Female

4. Child's Birthdate: |__|__| - |__|__| - |__|__|__|__| mm dd yyyy

Enter name and relationship code of the person being interviewed.

5a. Name: _____ _____ 5b. Relationship Code: |__|__|__|

001 - Mother of Child
002 - Father of Child
301 - Adoptive mother
302 - Adoptive father

Other: _____
Common codes are listed here. For other relationships, please look up relationship code from Appendix B of the Follow up Manual of Procedures and enter above.

6. Type of Interview: 1~ Face to Face 2~ Telephone

At this time, we would like a little information about the environment in which your new child will grow up.

7. First, how many people normally live with you in your home for at least 6 months of the year?

Total household members: |__|__|

8. After the first few months, will your child be sharing a room with other family members on a regular basis?

1~ Yes 2~ No

8a. IF YES: How many people will sleep in the same room with him/her? |__|__|

9. How many rooms are there in your house, excluding closets and bathrooms? |__|__|

10. Do you have any pets inside the home? 1~ Yes 2~ No *Skip to Question 11*
If YES, how many.....
10a. *check and record number:* 1~ Dogs in the home? |__|__|
2~ Cats in the home? |__|__|
3~ Other pets are in the home? |__|__| SPECIFY: _____

11. Does your home or apartment have air conditioning or some kind of cooling? 1~ Yes 2~ No *Skip to Question 12*
If YES,
11a. Air Conditioning? 1~ Yes 2~ No
11b. Evaporative Cooling? *(Desert Southwest)* 1~ Yes 2~ No
11c. Other? 1~ Yes 2~ No If YES, SPECIFY_____

12. How is your home heated? (IF MORE THAN ONE, PLEASE CHECK ALL THAT APPLY).
    1~ Steam or hot water (radiator)
    2~ Central gas furnace (furnace)
    3~ Electric
    4~ Wood Stove
    5~ Other SPECIFY: _____
    6~ Don't know

13. What one fuel is used most for cooking in your home?
    1~ Electricity
    2~ Gas
    3~ Fuel Oil
    4~ Wood Stove
    5~ Other SPECIFY: _____
    6~ Don't Know

The next questions are about your baby's diet.

14. Is your child receiving: (READ ALL CHOICES)
    1~ Only breast milk
    2~ Only formula *Skip to Question 15*
    3~ Both breast milk and formula *Skip to Question 15*

If answer to 14 is 1 (only breast milk)

a. Will this be supplemented with formula in the first 6 months?

1~ Yes 2~ No 3~ Don't Know

b. If yes, when will supplements begin? |___|___| months

15. Does the mother (you) plan to work outside the home within the next year?
    1~ Yes
    2~ No
    3~ Don't Know

The next questions are about smoke exposure.

16. Which one of the following 3 statements best describes the situation regarding smoking in your child's **home**? *Read all options to the interviewee before recording a response.*

1❑ Smoking is allowed in any common room of the home
2❑ Smoking is limited to part of the house where the child rarely goes
3❑ There is no smoking inside at all → 16a. Are there any exceptions to this situation?

1~ Yes 2~ No (Skip to Question 17)

16b. Under what circumstances are the exceptions allowed? SPECIFY:

_____

17. Which one of the following 5 statements best describes the situation regarding smoking in your **car**? *Read all options to the interviewee before recording a response.*
    1❑ Do not have a car
    2❑ Smoking is usually or always allowed
    3❑ Smoking is sometimes allowed
    4❑ Smoking occurs in the car only when the child is not inside
    5❑ There is no smoking inside the car → 17a. Are there any exceptions to this situation?

1~ Yes 2~ No (Skip to Question 18)

17b. Under what circumstances are the exceptions allowed? SPECIFY:

_____

18. How often has the baby's mother or primary caretaker (you) smoked since your child was born?

1~ Never 2~ Occasionally 3~ Daily

19. Altogether, how many people who live in the child's home smoke? |__|__| people

In the next section, we'd like to know what breathing and allergy problems run in the family. Administer attached Family History Questionnaire using the following script:

Mother or guardian:

We'll start with the baby's mother. How old is the baby's biologic mother? Does she have bronchitis, emphysema, COPD, bronchiectasis, asthma, inhaled allergies, or food allergies?

Does the baby's mother have any other chronic respiratory illness?

How often does this person smoke in the baby's home?

Father
For the baby's biologic father, is he living? How old is he? Does he have bronchitis, emphysema, COPD, bronchiectasis, asthma, inhaled allergies, or food allergies?

Does he have any other chronic respiratory illness?

How often does he smoke in the baby's home?

Complete the remainder of the table by collecting the same medical history using the scripting above.

20. Finally, which friend or relative is most likely to be able to contact you 6 months from now in case we lose contact with you?

_____ _____
Name Relationship

_____
Address

_____
Telephone

_____
Cell Phone

_____
Email

Thank you for your help in providing us with this important information, and for your continued participation in the Breathing Outcomes Study.

NICU Discharge-Baseline Interview
Family History Questionnaire

1. Relationship to enrolled child:	**Mother**	**Father**	**Maternal Grandmother**	**Maternal Grandfather**	**Paternal Grandmother**	**Paternal Grandfather**
2. Living?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
3. Age (in years):	_____	_____	_____	_____	_____	_____
4. Does this person have:						
a. COPD	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
b. Chronic Bronchitis?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
c. Emphysema?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
d. Bronchiectasis?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
e. Asthma?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
f. Inhaled Allergies?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
g. Food Allergies?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
h. Any other chronic respiratory disease? (SPECIFY)	1.Yes 2.No 3.DK _____ _____	1.Yes 2.No 3.DK _____ _____	1.Yes 2.No 3.DK _____ _____	1.Yes 2.No 3.DK _____ _____	1.Yes 2.No 3.DK _____ _____	1.Yes 2.No 3.DK _____ _____
5. How often does this person smoke in the baby's home*?	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently

Never = never; rarely = less than once per month; sometimes = once per month but less than once /week; frequently = once per week or greater
DK = Don't Know

NICHD SUPPORT Trial
Breathing Outcomes Study

Administered At 6 And 12 Months Corrected Age

This interview should be administered by a trained study interviewer for:

_____
(Child's name)

All questions pertain only to his/her health.

The parent or care giver, who completed the initial interview, should complete this survey and all future surveys. The interviewer will need to ask for that parent (see Manual of Operations).

Introduction Script:
When parent or primary care giver is on phone:

Hello, my name is <your name>. I am calling from the <NICHD Center>. As you probably remember, when you were in the NICU you enrolled in our study about respiratory health of premature infants. I am calling to ask you some questions about your baby's breathing. It will take about 10-20 minutes to complete. Is this a good time for you?

As with all information we collect, the answers to these questions will be kept confidential.

Before we begin this interview, it would be helpful if you could gather any notes you have about your baby's breathing as well as any medications your child has been prescribed or has been taking and have them in front of you. As with all information we collect, the answers to these questions will be kept confidential.

Center: ____ Site: ___ Network No. _____ SUPPORT Follow-up No. _____ Birth No. ___ Mother's Initials: _____

1. TODAY'S DATE: |__|__| - |__|__| - |__|__|__|__|
mm dd yyyy

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's Name:_____ _____
(first) (last)

Child's Birthdate: |__|__| - |__|__| - |__|__|__|__|
mm dd yyyy

Telephone Number _____-_____-_____

Address _____

_____

Which friend or relative is most likely to be able to contact you 6 months from now in case we lose contact with you?

_____ _____
Name Relationship

_____
Address

_____
Telephone

_____
Cell Phone

_____
Email

Enter name and relationship code of the person being interviewed:

2a. Name: _____ _____ 2b. Relationship Code: |__|__|__|

001 - Mother of Child
002 - Father of Child
301 - Adoptive mother
302 - Adoptive father

Other: _____
Common codes are listed here for other relationships, please look up relationship code from Appendix B of the Follow up Manual of Procedures and enter above.

3. Type of Interview: 1~ Face to Face 2~ Telephone

4. Location of Interviewer: 1~ Local Center (Option 1) 2~ Rochester (Option 2)

Instructions:
Parents or guardians expressing concerns regarding their child's breathing should be advised to discuss them with the family's primary care physician.

Where the phrase "last contact" is used below, please substitute with the most specific relevant time prompt, e.g. for the 6 month interview, refer to "since NICU discharge"; for the 12 month interview, refer to "over the past 6 months", etc.

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (__ __) months ago on (__ __/__ __/__ __) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing problems your child may have.

5. Has the child been with you during the past 6 months? 1~ Yes 2~ No

Since our last contact with you about your child.....

6. How many times has your child visited a doctor's office? |___|___| times

6a. How many of these times were because of wheezing or breathing problems? |___|___| times

Since our last contact with you about your child.....

7. How many times has your child visited an Emergency Department (Emergency room)? |___|___| times

7a. How many of these times were because of wheezing or breathing problems? |___|___| times

Since our last contact with you about your child.....

8. How many times has your child stayed in the hospital for one or more nights in a row? |___|___| times

8a. How many of these times were because of wheezing or breathing problems? |___|___| times

The next questions are about your baby's breathing.
The first question is about wheezing. By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical.

9. Since our last contact with you, has your baby's chest sounded wheezy or whistling?

1~ Yes 2~ No 3~ Don't know

Question 9a. "Has your baby's breathing sounded like this?" ***(play audio clip of wheezing).***

1~ Yes 2~ No 3~ Don't know If 2 or 3, SKIP TO QUESTION 10

IF **YES** TO QUESTION 9 or 9a:

9b. Has this occurred with colds?
1~ Yes
2~ No *Skip to c*
3~ Sometimes

9c. Has your child's chest sounded wheezy or whistling apart from colds?
1~ Yes
2~ No

9d. During what month did your child's chest first sound wheezy or whistling?

|___|___|months (enter calendar month, Jan = 01; Feb = 02); |___|___| Year

9e. Since our last contact with you, **on average**, how often has your child's chest sounded wheezy or whistling during:

The Daytime? Would you say...(e.1)	***The Nighttime? Would you say...(e.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

9f. Since our last contact with you, **during the worst 2 week period**, how often has your child's chest sounded wheezy or whistling during:

The Daytime? Would you say... (f.1)	***The Nighttime? Would you say...(f.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

9g. Since our last contact with you, has your child been diagnosed with wheezing by a doctor?
1~ Yes
2~ No

IF YES, BE SURE TO COMPLETE QUESTION 27

10. Since our last contact with you, has your child had a cough for more than 3 days when he/she did not have a cold?

1~ Yes 2~ No SKIP TO QUESTION 11

IF **YES** TO QUESTION 10

10a. At what time of the day has this cough usually occurred? (CHECK ALL THAT APPLY)

1~ In the morning, shortly after rising
2~ Later in the day
3~ During the night
4~ No relation to time of day

10b. Has he/she coughed on most days for as much as 2 to 3 months?

1~ Yes
2~ No

10c. During what month and year did your child first develop the cough?

|___|___|months (enter calendar month, Jan = 01; Feb = 02); |___|___| Year

10d. Has your child's chest ever sounded wheezy or whistling with episodes of coughing?

1~ Yes
2~ No

10e. Since our last contact with you, **on average**, how often has your child had coughing during:

The Daytime? Would you say... (e.1)	***The Nighttime? Would you say...(e.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

10f. Since our last contact with you, **during the worst 2-week period**, how often has your child had coughing?

The Daytime? Would you say... (f.1)	***The Nighttime? Would you say...(f.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

11. Since our last contact with you, **on average**, how many **days per month** did you have to change your daytime or evening plans because of your child's breathing problems:

1❑ None, we never had to change plans
2❑ More than none but less than 3 days
3❑ 3-6 days
4❑ 7 or more days

12. Since our last contact with you, **during the worst 2 week period**, how many **days** did you have to change your daytime or evening plans because of your child's breathing problems:

1❑ None, we never had to change plans
2❑ More than none but less than 3 days
3❑ 3-6 days
4❑ 7 or more days

13. Since our last contact with you, has your child had asthma, reactive airways disease or a BPD flare-up diagnosed by a doctor? 1~ Yes 2~ No

14. Since our last contact with you, has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?

1~ Yes 2~ No

15. Since our last contact with you, has your child had croup diagnosed by a doctor?
1~ Yes 2~ No

The next questions are about your baby's diet.

16. Since our last contact with you, did your baby receive mother's breast milk, either at breast, from a bottle or through a tube?

1~ Yes 2~ No If NO, skip to Question 17

If yes to Question 16:

16a. For how many months did your child receive breast milk feedings?
Would you say... 1~ Less than 1 month
2~ 1-3 months
3~ 4-6 months

16b. For how many months did your child receive breast milk for more than half of his/her feedings?
Would you say... 1~ Less than 1 month
2~ 1-3 months
3~ 4-6 months

The next questions are about smoke exposure.

17. Which one of the following 3 statements best describes the situation regarding smoking in your child's **home**? *Read all options to the interviewee before recording a response.*
1❑ Smoking is allowed in any common room of the home
2❑ Smoking is limited to part of the house where the child rarely goes
3❑ There is no smoking inside at all → 17a. Are there any exceptions to this situation?

1~ Yes 2~ No (Skip to Question 18)

17b. Under what circumstances are the exceptions allowed? SPECIFY:

_____

18. Which one of the following 5 statements best describe the situation regarding smoking in your **car**? *Read all options to the interviewee before recording a response.*
1❑ Do not have a car
2❑ Smoking is usually or always allowed
3❑ Smoking is sometimes allowed
4❑ Smoking occurs in the car only when the child is not inside
5❑ There is no smoking inside the car → 18a. Are there any exceptions to this situation?

1~ Yes 2~ No (Skip to Question 19)

18b. Under what circumstances are the exceptions allowed? SPECIFY:

_____

19. How often has the **mother or primary care giver** smoked since your child was born?

1~ Never 2~ Occasionally 3~ Daily

20. How many people in the child's home smoke? |___|___| people

The next questions are about your home and your babysitter's home or day care.

21. Approximately how many hours per week does your child spend at a babysitter's home or day care?
|___|___| hrs *If 0, skip to Question 22*

IF 21 is greater than 0:

21a. How frequent is there smoke exposure at the babysitter or daycare?
1~ Never 2~ Occasionally 3~ Daily 4~ Don't Know

21b. How many children beside your baby are in the daycare? | | | | children

22. How many children under 12 live in your house? |__|__| children

23. Do you have any pets inside the home? 1~ Yes 2~ No *Skip to Question 24*

23a. If YES, how many pets are there inside the home?
Check all that apply and record number: 1~ Dogs |__|__|
2~ Cats |__|__|
3~ Other |__|__| SPECIFY: _____

The last questions involve respiratory treatments that your baby may receive.

PROPHYLAXIS

24. Has your child had RSV shots to prevent Respiratory Syncytial Virus (Synagis, palivizumab, RSV shot)?

1~ Yes 2~ No 3~ Don't know

25. Has your child had a flu shot? 1~ Yes 2~ No 3~ Don't know

OXYGEN

26. Is your child on any oxygen therapy at home?

1~ Yes 2~ No Skip to Question 27

Indicate Yes or No for each			*lpm = liters per minute
26a. Oxygen cannula	1~ Yes	2~ No FiO2_____	lpm*_____
26b. Oxygen hood	1~ Yes	2~ No FiO2_____	lpm*_____
26c. Ventilator	1~ Yes	2~ No FiO2_____	lpm*_____

MEDICATIONS *(Enter responses in table. Do not prompt for each medication in the Medication Code List below.)*

The last two questions involve the medicines your child is taking for breathing problems.

27. Since our last contact with you, what medicines has your baby taken, including medicines delivered by a nebulizer or breathing machine at home?	27a. Code	27b. Does he/she take that medicine everyday, sometimes or only when sick? *(repeat for each medication)*
1		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
2		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
3		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
4		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
5		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
6		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
7		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

Medication Code List:

Rescue medicines:
1 Albuterol
2 Proventil
3 Serevent
4 Ventolin
5 Volmax
6 Xopenex

Other Inhaled medications:
7 Cromolyn (Intal)
8 Nedocromil (Tilade)

Inhaled steroids:
9 Advair
10 Aerobid
11 Azmacort
12 Beclovent
13 Flovent
14 Vanceril
15 Pulmicort

Systemic steroids:
16 Decadron
17 Prednisone
18 Prednisolone

Leukotriene blocker:
19 Accolate
20 Singulair

Methylxanthines:
21 Theophylline

Diuretic medications:
22 Diuril
23 Lasix
24 Aldactizide
25 Aldactone

Miscellaneous / Non-specific
26 Nebulizer
27 Other_____

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Breathing Outcomes Study.

NICHD SUPPORT Trial
Breathing Outcomes Study

Administered At 18-22 Months Corrected Age

This interview should be administered by a trained study interviewer. The target window for this interview is between 18-22 months' corrected age.

_____
(Child's name)

All questions pertain only to his/her health.

Introduction Script:
When parent or primary care giver is on phone:

Hello, my name is <your name>. I am calling from the <NICHD Center>. As you probably remember, when you were in the NICU you enrolled in our study about respiratory health of premature infants. I am calling to ask you some questions about your baby's breathing. It will take about 10-20 minutes to complete. Is this a good time for you?

As with all information we collect, the answers to these questions will be kept confidential.

Before we begin this interview, it would be helpful if you could gather any notes you have about your baby's breathing as well as any medications your child has been prescribed or has been taking and have them in front of you.

NICU Network	SUPPORT TRIAL Breathing Outcomes Study	SUPF03 Rel 1.0 October 12, 2005
	18-22 Month Interview	
Center: ___ Site: ___ Network No. _____	SUPPORT Follow-up No. _____ Birth No. ___	Mother's Initials: _____

1. TODAY'S DATE: |__|__| - |__|__| - |__|__|__|__|
mm dd yyyy

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's Name:_____ _____
(first) (last)

Child's Birthdate: |__|__| - |__|__| - |__|__|__|__|
mm dd yyyy

Telephone Number _____-_____-_____

Address _____

_____

Which relative is most likely to have your address in case we lose contact with you?

_____ _____
Name Relationship

_____
Address

_____
Telephone

_____
Cell Phone

_____
Email

Enter name and relationship code of the person being interviewed*:

2a. Name: _____ _____ 2b. Relationship Code: |__|__|__|

001 - Mother of Child
002 - Father of Child
301 - Adoptive mother
302 - Adoptive father

Other: _____
Common codes are listed here for other relationships, please look up relationship code from Appendix B of the Follow up Manual of Procedures and enter above.

3. Type of Interview: 1~ Face to Face 2~ Telephone

4. Location of Interviewer: 1~ Local Center (Option 1) 2~ Rochester (Option 2)

Instructions:
Parents or guardians expressing concerns regarding their child's breathing should be advised to discuss them with the family's primary care physician.

Where the phrase "last contact" is used below, please substitute with the most specific relevant time prompt, e.g. for the 18-22 month interview, refer to "over the past 6 months", etc.

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (__ __) months ago on (__ __/__ __/__ __) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing problems your child may have.

5. Has the child been with you over the past 6 months? 1~ Yes 2~ No

Since our last contact with you about your child...

6. How many times has your child visited a doctor's office? |__|__| times

6a. How many of these times were because of wheezing or breathing problems? |__|__| times

Since our last contact with you about your child...

7. How many times has your child visited an Emergency Department (Emergency room)? |__|__| times

7a. How many of these times were because of wheezing or breathing problems? |__|__| times

Since our last contact with you about your child...

8. How many times has your child stayed in the hospital one or more nights in a row? |__|__| times

8a. How many of these times were because of wheezing or breathing problems? |__|__| times

The next questions are about your baby's breathing.

The first question is about wheezing. By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical. It can sound like this,..... (play audio clip of wheezing).

9. Since our last contact with you, has your baby's chest sounded wheezy or whistling?

1~ Yes 2~ No 3~ Don't know If 2 or 3, SKIP TO QUESTION 10

Question 9a. "Has your baby's breathing sounded like this?" ***(play audio clip of wheezing).***

1~ Yes 2~ No 3~ Don't know If 2 or 3, SKIP TO QUESTION 10

IF **YES** TO QUESTION 9 or 9a:

9b. Has this occurred with colds?
1~ Yes
2~ No *Skip to c*
3~ Sometimes

9c. Has your child's chest sounded wheezy or whistling apart from colds?
1~ Yes
2~ No

9d. During what month and year did your child's chest first sound wheezy or whistling?

|___|___|months (enter calendar month, Jan = 01; Feb = 02); |___|___| Year

9e. Since our last contact with you, **on average**, how often has your child's chest sounded wheezy or whistling during:

The Daytime? Would you say...(e.1)	***The Nighttime? Would you say...(e.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

9f. Since our last contact with you, **during the worst 2 week period**, how often has your child's chest sounded wheezy or whistling during:

The Daytime? Would you say... (f.1)	***The Nighttime? Would you say...(f.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

9g. Since our last contact with you, has your been diagnosed with wheezing by a doctor?
1~ Yes
2~ No

10. Since our last contact with you, has your child had a cough for more than 3 days when he/she did not have a cold?

1~ Yes 2~ No SKIP TO QUESTION 11

IF **YES** TO QUESTION 10

10a. At what time of the day has this cough usually occurred?
(CHECK ALL THAT APPLY)

1~ In the morning, shortly after rising
2~ Later in the day
3~ During the night
4~ No relation to time of day

10b. Has he/she coughed on most days for as much as 2 to 3 months?

1~ Yes
2~ No

10c. During what month and year did your child first develop the cough?

|___|___|months (enter calendar month, Jan = 01; Feb = 02); |___|___| Year

10d. Has your child's chest ever sounded wheezy or whistling with episodes of coughing?

1~ Yes
2~ No

10e. Since our last contact with you, **on average**, how often has your child had coughing during:

The Daytime? Would you say... (e.1)	***The Nighttime? Would you say...(e.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

10f. Since our last contact with you, **during the worst 2-week period**, how often has your child had coughing?

The Daytime? Would you say... (f.1)	***The Nighttime? Would you say...(f.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

11. Since our last contact with you, **on average**, how many **days per month** did you have to change your daytime or evening plans because of your child's breathing problems:

1❑ None, we never had to change plans
2❑ More than none but less than 3 days
3❑ 3-6 days
4❑ 7 or more days

12. Since our last contact with you, **during the worst 2 week period**, how many **days** did you have to change your daytime or evening plans because of your child's breathing problems:

1❑ None, we never had to change plans
2❑ More than none but less than 3 days
3❑ 3-6 days
4❑ 7 or more days

13. Since our last contact with you, has your child had asthma, reactive airways disease or a BPD flare-up diagnosed by a doctor? 1~ Yes 2~ No

14. Since our last contact with you, has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?
1~ Yes 2~ No

15. Since our last contact with you, has your child had croup diagnosed by a doctor?
1~ Yes 2~ No

The next question are about your baby's diet.

16. Since our last contact with you, did your baby receive mother's breast milk, either at breast, from a bottle or through a tube?

1~ Yes 2~ No If NO, skip to Question 17

If yes to Question 16:

16a. For how many months did your child receive breast milk feedings?
Would you say... 1~ Less than 1 month
2~ 1-3 months
3~ 4-6 months

16b. For how many months did your child receive breast milk for more than half of his/her feedings?
Would you say... 1~ Less than 1 month
2~ 1-3 months
3~ 4-6 months

The next questions are about smoke exposure.

17. Which one of the following 3 statements best describes the situation regarding smoking in your child's **home**? *Read all options to the interviewee before recording a response.*
1❑ Smoking is allowed in any common room of the home
2❑ Smoking is limited to part of the house where the child rarely goes
3❑ There is no smoking inside at all → 17a. Are there any exceptions to this situation?

1~ Yes 2~ No (Skip to Question 18)

17b. Under what circumstances are the exceptions allowed? SPECIFY:

_____

18. Which one of the following 5 statements best describes the situation regarding smoking in your **car**? *Read all options to the interviewee before recording a response.*
1❑ Do not have a car
2❑ Smoking is usually or always allowed
3❑ Smoking is sometimes allowed
4❑ Smoking occurs in the car only when the child is not inside
5❑ There is no smoking inside the car → 18a. Are there any exceptions to this situation?

1~ Yes 2~ No (Skip to Question 19)

18b. Under what circumstances are the exceptions allowed? SPECIFY:

_____

19. How often has the **mother or primary care giver** smoked since your child was born?

1~ Never 2~ Occasionally 3~ Daily

20. How many people in the child's home smoke? |___|___| people

The next questions are about your home and your babysitter's home or day care.

21. Approximately how many hours per week does your child spend at a babysitter's home or day care?
|___|___| hrs If 0 skip to question 22.

IF 21 is greater than 0:

21a. How frequent is there smoke exposure at the babysitter or daycare?
1~ Never 2~ Occasionally 3~ Daily 4~ Don't Know

21b. How many children beside your baby are in the daycare? |___|___|___| children

22. How many children under 12 live in your house? |___|___| children

23. Do you have any pets inside the home? 1~ Yes 2~ No Skip to Question 24

23a. If YES, how many pets are there inside the home?
Check all that apply and record number: 1~ Dogs |___|___|
2~ Cats |___|___|
3~ Other |___|___| SPECIFY: _____

The last questions involve respiratory treatments that your baby may receive.

PROPHYLAXIS

24. Has your child had RSV shots to prevent Respiratory Syncytial Virus (Synagis, palivizumab RSV, shot)?

1~ Yes 2~ No 3~ Don't know

25. Has your child had a flu shot? 1~ Yes 2~ No 3~ Don't know

OXYGEN

26. Is your child on any oxygen therapy (oxygen tank) at home?

1~ Yes 2~ No Skip to Question 27

Indicate Yes or No for each				*lpm = liters per minute
a. Oxygen cannula	1~ Yes	2~ No	FiO2_____	lpm*_____
b. Oxygen hood	1~ Yes	2~ No	FiO2_____	lpm*_____
c. Ventilator	1~ Yes	2~ No	FiO2_____	lpm*_____

MEDICATIONS *(Enter responses in table. Do not prompt for each medication in the Medication Code List below.)*

The next questions involve the medicines your child is taking for breathing problems.

27. Since our last contact with your, what medicines has your baby taken, including medicines taken by a nebulizer or breathing machine at home?	27a. Code	27b. Does he/she take that medicine everyday, sometimes or only when sick? *(repeat for each medication)*
1		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
2		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
3		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
4		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
5		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
6		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
7		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

Medication Code List:

Rescue medicines: 1 Albuterol 2 Proventil 3 Serevent 4 Ventolin 5 Volmax 6 Xopenex *Other Inhaled medications:* 7 Cromolyn (Intal) 8 Nedocromil (Tilade) *Inhaled steroids:* 9 Advair 10 Aerobid 11 Azmacort 12 Beclovent 13 Flovent 14 Vanceril 15 Pulmicort	*Systemic steroids:* 16 Decadron ~~17~~17 Prednisone 18 Prednisolone *Leukotriene blocker:* 19 Accolate 20 Singulair *Methylxanthines:* 21 Theophylline *Diuretic medications:* 22 Diuril 23 Lasix 24 Aldactizide 25 Aldactone Miscellaneous / Non-specific 26 Nebulizer 27 Other_____

Formatted: Bullets and Numbering

The next 2 questions are about respiratory infections.....

28. **During the past year**, for how many days has your child been unable to do his/her usual activities because of illnesses such as chest (not head) colds, bronchitis, asthma or pneumonia?
   1❑ 0-3 per year
   2❑ 4-5 per year
   3❑ 6-9 per year
   4❑ more than 9 per year

29. **During the past year**, how many head colds (common colds) has your child had? Would you say...
   1❑ 0-3 per year
   2❑ 4-5 per year
   3❑ 6-9 per year
   4❑ more than 9 per year

The last questions are about allergies.

30. Has your child **ever** had hay fever or any other condition that makes his/her nose runny, stuffy, or itchy **apart** from colds? 1~ Yes 2~ No

31. Has your child **ever** had allergies which cause nose, eye or lung problems?
   1~ Yes 2~ No

32. Has your child **ever** been allergic to any food?
   1~ Yes 2~ No

33. Has he/she **ever** been allergic to any medicine?
   1~ Yes 2~ No

34. Has your child **ever** had eczema (allergic skin rash)?

1~ Yes 2~ No (End of Interview)

34a. Was eczema diagnosed by a doctor?

1~ Yes 2~ No

End of Interview

THANK YOU FOR YOUR COOPERATION

SUPPORT Trial

Breathing Outcomes~~Pulmonary Outcomes Follow-up~~ Study

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial)

NICHD Neonatal Research Network

Manual of Operations

~~November 1, 2005~~November 3, 2005

TABLE OF CONTENTS

Chapter 1
Overview and Trial Design

1.1 Introduction

This manual provides detailed instructions of study procedures for the Breathing Outcomes~~Follow-up~~ Study of the NICHD SUPPORT Trial ~~Pulmonary Outcomes Follow-up Study~~ (The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants). This manual should be used as a reference guide for study staff including investigators, coordinators, and data managers. The trial objectives and design are summarized briefly below. For further discussion to the study background and design, please refer to the Breathing Outcomes~~Follow-up~~ Study Protocol.

1.2 Study Design

This study is a longitudinal follow-up of surviving infants enrolled, randomized and treated as part of the SUPPORT Trial, which was a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This follow-up study will determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the incidence of symptomatic airway dysfunction (defined as recurrent wheezing or chronic cough) and volume of outpatient care in the first 18-22 months' corrected age (CA). The individual factors to be tested in this follow-up study are:

1) Symptomatic airway dysfunction and need for outpatient pulmonary care in the first 18-22 months among infants managed with a lower SpO2 range (85% to 89%) as compared to a higher, more conventional SpO2 range (91% to 95%).

2) Symptomatic airway dysfunction and need for outpatient pulmonary care in the first 18-22 months corrected age among infants managed with CPAP and a permissive ventilatory strategy versus infants managed with prophylactic surfactant and conventional ventilation begun in the delivery room and continuing in the NICU.

Table 1 below describes the study treatment groups. Refer to the SUPPORT Trial Protocol for further details regarding the projected outcomes relative to the study interventions

Table 1: SUPPORT Trial Study Treatment Groups

Randomized Intervention	**Low SpO2 85% to 89%**	**High SpO2 91 to 95%**
Treatment **Early CPAP**	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control **Prophylactic/Early Surfactant**	Control + Low SpO2	Control + High SpO2

1.3 Primary Hypotheses

1) We hypothesize that relative to infants managed with a higher SpO2 range (91% to 95%),

infants managed with a lower SpO2 range (85% to 89%) will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care at 18-22 months' CA.

2) We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

1.4 Secondary Hypotheses

1) We hypothesize that **among infants with CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

2) We hypothesize that **among infants without CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

1.5 Summary of Data Forms

The following is a summary of the data forms used in this study. Further details on each form are provided in subsequent chapters. A complete set of forms can be found in Appendix A.

NICU Discharge-Baseline Interview (SUPF01)
This interview will be administered to the parent or guardian by trained study ~~staff~~ staff prior to NICU discharge or within 30 days after NICU discharge. For patients enrolled into the Breathing Outcomes Study after NICU discharge, this questionnaire can be administered prior to the 6 month questionnaire. Questions concerning family medical history, anticipated living arrangements, and alternate contact information will be asked.

The purpose of the discharge questionnaire is to assure adequate randomization of important covariates affecting outpatient respiratory health and to obtain baseline data on home environment and family history of respiratory diseases.

6 Month and 12 Month Interview (SUPF02)
This interview will be administered by telephone or face to face to the parent or guardian by a trained ~~telephone~~ interviewer at 6 months' CA and again at 12 months' CA.

The purpose of these questionnaires is to obtain an **interval** respiratory history. Questions are designed to collect respiratory history since the last contact with the interviewee, such that when the 6, 12 and 18-22 month questionnaires are taken together, a complete respiratory history over the time period is collected.

18-22 Month Interview (SUPF03)

This interview will be administered to the parent or guardian at 18-22 months CA by either telephone interview prior to the regularly scheduled 18-22 month NICHD developmental follow up clinic visit or face to face at the time of the visit.

The purpose of these questionnaires is to obtain an **interval** respiratory history and to identify environmental exposures that may increase the likelihood of symptomatic airway dysfunction.

Chapter 2
Administration

2.1 Organizational Structure

The NICHD Neonatal Research Network is conducting this study. The Network is funded by the NICHD under cooperative agreements with seventeen institutions comprised of sixteen clinical centers and a data coordinating center. The Steering Committee for the Network consists of the Principal Investigator from each clinical center, the data center, and the NICHD project officer. The Steering Committee Chairman is appointed by NICHD and is not a Principal Investigator from any of the Clinical Centers.

SUPPORT Trial Follow-up Subcommittee

The SUPPORT Protocol Subcommittee is responsible for the preparation and maintenance of the protocol, data forms, and manual of operations. This subcommittee will monitor the overall study performance (including protocol compliance) and will report the progress of the trial to the Steering Committee. SUPPORT Subcommittee members are:

Neil Finer, MD

Waldemar A. Carlo, MD,

Edward F. Donovan MD

Michele Walsh, MD

Shahnaz Duara, MD

Rosemary D. Higgins, MD

Abhik Das, PhD

Ruth Everett, RN

Wade Rich, RRT

In addition, Dr. Vohr, as director of the Follow Up Program, will coordinate input from the Follow Up PIs. Timothy P. Stevens, MD, MPH and Peter Szilagyi, MD, MPH from the Department of Pediatrics at the University of Rochester will be instrumental in designing; implementing and executing the clinical studies outlined here and will have significant ongoing involvement with the project.

2.2 Participating NICHD Neonatal Research Network Centers

Centers from the NICHD Neonatal Research Network participating in the trial are listed below. The NICHD center number is indicated in parentheses next to the name of each center. The Neonatal Research Network principal investigators (PIs) are located in the second column, the Follow-up PIs in the third column and the SUPPORT Study PIs in the fourth column.

PARTICIPATING CENTERS	NRN PI	NRN Follow Up PI	SUPPORT STUDY PI
Case Western Reserve Univ. (3) Rainbow Babies and Children's Hospital	Michele Walsh, MD	Dee Wilson, MD	Michele Walsh, MD
University of Texas-Dallas (4)	Charles Rosenfeld, MD	Roy Heyne, MD	Walid Salhab, MD
Wayne State University (5) Children's Hospital of Michigan	Seetha Shankaran, MD	Yvette Johnson, MD	Seetha Shankaran, MD
University of Miami (8) Jackson Memorial Hospital	Shahnaz Duara, MD	Charles Bauer, MD	Shahnaz Duara, MD
Emory University (9) Grady Memorial Hospital	Barbara J. Stoll, MD	Ira Adams-Chapman, MD	Susie Buchter, MD
University of Cincinnati (11) University of Cincinnati Hospital	Edward F. Donovan, MD	Jean Steichen, MD	Vivek Narendran, MD Kurt Schibler, MD
Indiana University (12)	James A. Lemons, MD	Anna M. Dusick, MD	Brenda Poindexter, MD
Yale University (13) The Children's Hospital at Yale – New Haven	Richard A. Ehrenkranz, MD	~~Linda Mayes~~Richard A. Ehrenkranz, MD	Vineet Bhandari, MD
Brown University (14) Women and Infant's Hospital	William Oh, MD	Betty R. Vohr, MD	Abbot Laptook, MD
Stanford University (15) Stanford University Med Center	David K. Stevenson, MD	Susan R. Hintz, MD	Krisa Van Meurs, MD
University of Alabama (16) University of Alabama at Birmingham	Waldemar A. Carlo, MD	Myriam Peralta, MD	Waldemar A. Carlo, MD
University of Texas- Houston (18)	Jon E. Tyson, MD	Jon Tyson, MD	Brenda Morris, MD
Duke University (19)	Ronald Goldberg, MD	Ricki Goldstein, MD	C. Michael Cotten, MD
Wake Forest University (20)	Michael O'Shea, MD	Robert Dillard, MD	Michael O'Shea, MD
Golisano Children's Hospital at Strong (21) University of Rochester	Dale L. Phelps, MD	Gary Myers, MD	Nirupama Laroia, MD
University of California-San Diego (22)	Neil Finer, MD	Yvonne Vaucher, MD	Neil Finer, MD

2.3 Responsibilities of Clinical Centers

The minimum staff required for network participation at each clinical center is the physician Principal Investigator (PI), the Research Coordinator, and telephone interviewers, if interviews are not conducted by the Research Coordinator.

The research coordinator may identify another individual to conduct the telephone interviews. In this situation, it will be the coordinator's responsibility to assure that the interviewer is certified in standardized administration of the questionnaire (see below). The responsibilities of these individuals are described briefly in this chapter and in more detail in subsequent chapters.

The PI or designee is responsible for ensuring the proper conduct of the trial at his or her clinical center (including recruitment and treatment of patients as specified in the protocol), accurate collection of data and transmission of information to the Data Coordinating Center (DCC). Other specific duties include the following:

- Presenting an in-service to the other physicians
- Applying for IRB approval
- Introducing the study to the parents of prospective patients, and obtaining signed informed consent from the parents of eligible infants (in some centers this responsibility may be delegated)
- Reviewing all infants for whom informed consent has been obtained to confirm their eligibility
- Informing the IRB of the study progress.

The Research Coordinator will be responsible for the day-to-day operations of the study at the clinical center, including data collection and management. This responsibility includes the following:

- Collecting information necessary to complete the data collection forms, and coordinating data entry
- Training and certifying the staff in the use of the network computer
- Controlling access to the network computer and ensuring that required back-up, security and confidentiality are maintained
- Responding to edit messages and other communications from the data center
- Distributing updates of the protocol and of the manual of operations to clinical center staff
- Further responsibilities are based on the study administration option chosen by the center.

2.3.1 Delineation of Responsibilities by Study Administration Option

Clinical Centers have the option of administering the follow-up questionnaires to their own patients (Option 1) or having telephone interviewers of the University of Rochester Health Services Research Group administer the follow-up questionnaires to their patients (Option 2). Table 2 indicates which option the centers have chosen.

Table 2. **SUPPORT Trial - Breathing~~Pulmonary~~ Outcomes Study**

NICHD Site	*6, 12 and 18-22 Month Pulmonary Questionnaires Administered By*	Option Number
Alabama	Alabama	1
Brown	Brown	1
Cincinnati	Cincinnati	1
CWRU	CWRU	1
Dallas	Dallas	1
Duke	Duke	1
Emory	Rochester	2
Houston	Rochester	2
Indiana	Rochester	2
Miami	Miami	1
Rochester	Rochester	2
Stanford	Rochester	2
UCSD	UCSD	1
Wake Forest	Wake Forest	1
Wayne State	Wayne State	1
Yale	Yale	1

Regardless of the option chosen, each local center is responsible for obtaining informed consent, administering the NICU Discharge-Baseline Interview (SUPF01) and distributing the respiratory ~~diary~~brochure to parents, as well as tracking patients following discharge. Table 3 further describes the responsibilities of the local center and Rochester in Option 1 and Option 2.

Table 3.	Option 1	Option 2	
	Local Center	Local Center	Rochester
Consent / IRB	✓	✓	
Questionnaire at Discharge	✓	✓	
Patient Tracking	✓	✓	
Questionnaire at 6 & 12 mo.	✓		✓
Questionnaire at 18-22 mo.	✓		✓
Data Entry (questionnaires)	✓		✓

Each of the responsibilities discussed in table 3 above will be discussed separately below.

2.3.2 Consent

For both options, every effort will be taken to enroll ALL SUPPORT patients into the Breathing~~Pulmonary~~ Outcomes Study, including both currently enrolled SUPPORT patients (both patients still in NICU and those discharged from the NICU) and all future enrollees. By obtaining pulmonary outcome data for both current and future SUPPORT patients, death or adverse pulmonary outcome can be analyzed as competing outcomes. Sample consent forms for currently enrolled and future SUPPORT patients are attached.

2.3.3 Discharge Questionnaire

The purpose of the discharge questionnaire is to assure adequate randomization of important covariates affecting outpatient respiratory health and to obtain baseline data on home environment and family history of respiratory diseases. There are a total of 16 questions on the questionnaire; 9 questions on home environment and exposures, 1 question on alternate contact information, 6 questions on family history of allergy and respiratory problems.

Each center, regardless of study option chosen, will administer the discharge questionnaire. This will allow ascertainment of baseline data as well as confirming contact information for the family. For patients enrolled into the ~~Pulmonary~~ Breathing Outcomes ~~Follow up~~ Study after NICU discharge, this questionnaire can be administered prior to the 6 month questionnaire.

After completing the discharge – baseline questionnaire, parents ~~should~~ will be given the respiratory ~~diary~~ brochure ("My Baby's Breathing Book") ~~and instructed to record~~which will ask them to note how often their baby has wheezing or coughing, whether the baby visited a doctor's office, emergency room or was hospitalized for breathing problems. ~~Parents should be asked to gather the diary and any medications or other information about their baby's breathing when the interviewer calls in six months.~~ By presenting the brochure to the family and discussing it with them as they leave the NICU, each family will have opportunity to review the study with study personnel. This is especially important because many families will have committed to the follow up study several months before discharge. When the interviewer calls in six months, parents should be asked to gather any notes, medications or other information about their baby's breathing.

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2.3.4 Tracking

All centers (Option 1 and 2 centers) will track their own patient's telephone and contact information for the purpose of administering telephone questionnaires at 6, 12 and 18-22 months. This will also help assure attendance at the routine NICHD neurodevelopmental follow up clinic visit 18-22 months.

The following core set of contact information is recommended for all enrolled patients.

- Network number
- Patient Name
- DOB
- Gender
- Name of Prior Interview Respondent (if different than primary care taker)
    - Primary Caretaker Contact Information
        - Name
        - Relationship to patient
        - Mailing address
        - Telephone number #1
        - Telephone number #2
    - Secondary (Backup) Caretaker Information
        - Name
        - Relationship to patient
        - Mailing address
        - Telephone number #1
        - Telephone number #2

2.3.5 Responsibility of Option 1 Centers In Administering Questionnaires at 6, 12 And 18 Months' Corrected Age

Clinical Centers will have the option of administering the follow-up questionnaires to their own patients (Option 1) or having telephone interviewers from the University of Rochester Health Services Research Group administer the follow-up questionnaires to their patients (Option 2).

- Standardization of Interview Technique
  - In order to assure that interviews are administered in a standard and consistent manner, the University of Rochester Health Services Research Group will conduct an Interviewer Certification Program to train interviewers at Option 1 centers and Rochester based interviewers. All interviews must be performed by certified interviewers (see 2.4.7 below).

- Conducting the Interviews
  - Prior to each interview, a postcard will be mailed to the family reminding them to expect a telephone call.
  - For centers that see patients in an office setting, the questionnaire may be administered face to face.

2.3.6 Responsibility of Option 2 Centers In Administering Questionnaires at 6, 12 And 18 Months' Corrected Age

- Upon receipt of RTI reminder, Option 2 Centers will send a postcard to the family reminding them to expect a telephone call.
- Review and update contact information as necessary and fax contact information to the Rochester Health Services Research Group (RHSRG).
- The RHSRG will conduct the telephone interview.
- At the conclusion of each interview, contact information will be confirmed and updated contact information faxed back to the Option 2 Center.

2.3.7 Responsibilities of the University of Rochester Health Services Research Group

- The certification program will consist of two parts.
  - Part 1 - a teleconference training session during which each question on the questionnaires is reviewed and discussed with the interviewers. The goal is to assure that interviewers understand the purpose of each question and, in a standard way, how to deliver the question, elicit an answer and record the interviewee's response.

  - Part 2 will consist of a practice interview in which interviewers from each center interview the Rochester trainer, who simulates a standardized patient. Following the practice interview, the Rochester trainer and practice interviewer will discuss the interview and give feedback.

- Other responsibilities include:
  - Development and distribution of an audio clip of wheezing to be presented along with a verbal definition to the interview respondent to standardize interpretation of wheezing and to minimize ascertainment biases due to language, culture, literacy or interviewing techniques.
  - Maintaining trained Spanish-speaking individuals to conduct the telephone interviews with Spanish-speaking participants from centers choosing Rochester to administer the questionnaire to their patients (Option 2).
  - Spanish language versions of the questionnaires will be created and made available to all centers. The Cornell Translation Service, a University based professional translation service, will be contracted by the University of Rochester to perform the translation.

2.4 Responsibilities of the Data Coordinating Center

The DCC at RTI International is responsible for all aspects of statistical design and analysis as well as data management of the study. In particular, this includes:

- Processing, updating and distributing the protocol and manual of operations
- Developing and distributing the data forms, including periodic updates as necessary
- Developing, testing and implementing the database and other software. Ensuring that data are correct and complete by implementing editing and auditing procedures
- Monitoring the progress and quality of the study
- Preparing interim and final analyses and reports
- Participating in the preparation of presentations and publications relating to the study

The DCC is also responsible for sending monthly reminder reports to Network Centers. For patients enrolled in the Pulmonary Outcomes Study, the DCC will send a monthly reminder to each center with a list of IDs that are due to have questionnaires conducted. The report will include the following:

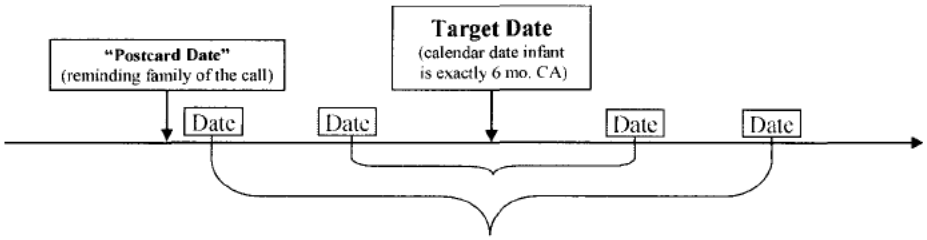
- Network number
- Gestational age
- Gender
- Date of last interview
- Care taker (relationship code) providing the previous interview
- Whether the previous interviews were conducted face to face or by telephone
- List of the 4 interviews that have been completed (CA = corrected age)
- Completed interview dates, dates of previous interviews and interviewee information may be presented as outlined in the table below.

Example table

Example table

Required Interviews	Date	Caretaker Interviewed	Face to Face?
▪ Discharge	__/__/__	_____	Y or N
▪ 6 month CA	__/__/__	_____	Y or N
▪ 12 month CA	__/__/__	_____	Y or N
▪ 18-22 month CA	__/__/__	_____	Y or N

- Target date for the current interview with windows within which interview should be accomplished, goal window (target date ± 2 weeks) and acceptable window (target date ± 4 weeks)
- A "postcard date", 5 weeks prior to the contact, when a postcard might be sent to the family reminding them of the upcoming call or visit



2.5 Responsibilities of NICHD

In addition to its role as a funding agency, the NICHD participates in the activities of the cooperative agreement by being represented on the Steering Committee. The Program Official also participates in the development of protocol and in assisting the Steering Committee in the coordination of the studies conducted by the Network. The NICHD Program Official, in conjunction with the RTI Principal Investigator is responsible for monitoring site performance of all participating centers. The Program Official has the following responsibilities:

- Assistance in the development of the study protocol.
- Assistance in the development of capitation-based budgets, including the identification of study costs and special institutional needs.
- Allocation of network resources to meet study needs.
- Facilitation of training meetings, site visits, and subcommittee meetings.
- Participating in preparation of publications.

Chapter 3
Screening, Eligibility, Consent

3.1 Study Population

This follow-up study will include all surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial, which were inborn infants of 24 0/7ths to 27 6/7th weeks at birth for which a decision was made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) were enrolled.

Inclusion Criteria

- Enrollment in the SUPPORT Trial
- Survival to hospital discharge
- Consent for enrollment into the Breathing~~Pulmonary~~ Outcomes ~~Follow-up~~ Study, obtained either at the time of enrollment into the SUPPORT Trial or separately.

3.2 Exclusion Criteria

- Refusal of informed consent

3.3 Informed Consent

Every effort will be taken to enroll ALL SUPPORT Trial patients into this follow-up study, including currently enrolled SUPPORT patients (both patients still in NICU and those discharged) and future enrollees. By obtaining pulmonary outcome data for both current and future SUPPORT patients, death or adverse pulmonary outcome can be analyzed as competing outcomes. Each local center will be responsible for obtaining informed consent for the Breathing Outcomes~~Follow-up~~ Study regardless of whether they are administering the follow-up questionnaires to their patients or Rochester is conducting the telephone interviews.

For future enrollees in the SUPPORT Trial, consent for the Breathing Outcomes~~Follow-up~~ Sstudy will be obtained at the time of enrollment in the main trial. As described in the SUPPORT Trial Manual of Operations, these infants will be recruited for the study by approaching one or both parents at the time of admission to the hospital at risk for premature delivery at 27 weeks or less. It is anticipated that, whenever possible, the parents will be approached by study personnel to discuss the trial and obtain an informed consent for the participation of the infant at delivery. Randomization will be by family, thus all offspring will be randomized to the same trial arms, provided adequate equipment and personnel are available at the time of delivery. Sample consent forms for currently enrolled and future SUPPORT patients are attached (Appendix C).

A Study Brochure will be given to each family at the time of the discharge interview. The brochure reviews the study and its commitments and also asks families to make observations about the baby's breathing symptoms and treatments. Reviewing the brochure is especially

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important because many families will have committed to the follow up study several months before discharge.

3.4 Screening Procedures

This follow-up study will include all surviving infants enrolled, randomized and treated as part of the NICHD Neonatal Research Network SUPPORT Trial.

For future enrollees in the SUPPORT Trial, all admissions for threatened premature delivery will be screened on a daily basis to ensure that eligible patients can be enrolled. Obstetrical colleagues at each participating institution will be informed of the nature of this study and encouraged to discuss this study with their patients at risk of premature delivery. The study coordinator at each site will maintain a screening log of potentially eligible patients. In addition, the usual practice of neonatal consultation for all such at risk deliveries will provide a second opportunity to approach mothers with fetuses at risk of preterm delivery.

Chapter 4
Randomization

4.1 Randomization Procedures

Randomization for the NICHD Neonatal Research Network SUPPORT Trial was stratified by gestational age group (24 - 25 6/7 and 26 - 27 6/7) and occurred prior to delivery for consented deliveries. The randomizations were performed by utilizing specially prepared envelopes. The Data Center prepared brown sealed envelopes which contained the identity of the treatment combination that were assigned to the infants enrolled into the study. Deliveries were randomized as a unit, thus multiples, twins, triplets etc were randomized to the same arm of the trial. One envelope corresponded to the delivery of a consenting mother regardless of the number of babies delivered so that all babies from a given delivery received the same treatment combination.

Refer to Section 4.1.1 of the NICHD Neonatal Research Network SUPPORT Trial Manual of Operations (MOO) for more information on randomization and masking as well as storing and assigning oximeters that occurred during the main study.

During the Breathing Outcomes~~Follow-up~~ Study activities, research coordinators and telephone interviewers, if different from the research coordinators, will remain blinded as to whether infants were randomized to the control or treatment group.

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Chapter 5
~~Follow-up~~Breathing Outcomes Study Procedures

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5.1 SUPPORT Trial Study Interventions

Refer to Chapter 5 of SUPPORT Trial Manual of Operations (MOO) for more information on the study interventions and the procedures for the treatment groups. The same questionnaires will be administered to both treatment groups in the ~~Follow-up~~ Breathing Outcomes Study.

5.2 ~~Pulmonary Follow Up~~Breathing Outcomes Study Interventions

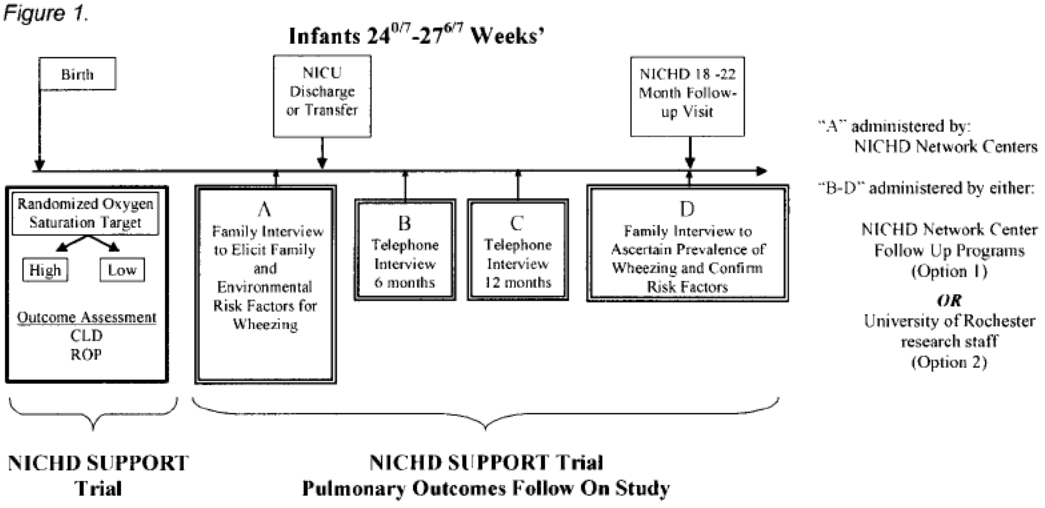
Before delivery, infants will be randomized according to the 2x2 factorial design of the SUPPORT Protocol.

The SUPPORT ~~Follow-up Study of Pulmonary~~Breathing Outcomes Study begins just prior to NICU discharge. See Figure 1 for a diagram of the SUPPORT Trial ~~Follow-up~~Breathing Outcomes Study procedures.

Four questionnaires will be administered at approximately 6 month intervals until the baby is 18-22 months' corrected age according the schedule outlined in Figure 1. Each interview will collect a 6 month interval history, which, when taken together, will provide a complete respiratory history over the first 18-22 months' corrected age. If a questionnaire is not completed, the subsequent questionnaire will include the full interval history since the last completed questionnaire.

SUPPORT Trial Follow-up Study

Figure 1.



DESCRITION OF QUESTIONNAIRES

A) Discharge Questionnaire Administered by Network Centers

The discharge interview consists of a primary caretaker (parent or guardian) interview to elicit family and environmental risk factors for wheezing and cough. The family interview will be administered at each participating Network Center by site study nurses prior to NICU discharge or transfer. The questions are based on intake questions used by the Tucson Respiratory Study and are designed to elicit family history of asthma, atopy, and home environmental exposures and to identify likely care givers. This interview will be administered to the parent or guardian by trained study staff prior to NICU discharge or within 30 days after NICU discharge. For patients enrolled into the Breathing Outcomes Study after NICU discharge, this questionnaire can be administered prior to the 6 month questionnaire.

The purpose of the discharge questionnaire is to assure adequate randomization of important covariates affecting outpatient respiratory health and to obtain baseline data on home environment and family history of respiratory diseases. There are a total of ~~16~~ 25 questions on the questionnaire; the first 6 are demographic, ~~9~~ 11 questions are on home environment and exposures, 2 questions are on diet, 1 question is on alternate contact ~~information,~~information, and a separate 5 ~~6~~ questions are on family history of allergy and respiratory problems.

Each center, regardless of study option chosen, will administer the discharge questionnaire and perform data entry. This will allow ascertainment of baseline data as well as confirming contact information for the family.

B) Respiratory History Questionnaires Administered at 6 and 12 Months' Corrected Age

The purpose of this questionnaire is to obtain an **interval** respiratory history. Questions are designed to collect respiratory history in areas outlined in the table at right. For centers choosing Option 1, interviews may be conducted either by telephone or face to face. For centers choosing Option 2, interviews will be conducted long distance by telephone from The Rochester Health Services Research Group to the family.

Outcome	Question No.
Respiratory Symptoms	9, 10, 13-15
Quality of Life	11, 12
Health Services Utilization	
Office	6
Emergency Department	7
Hospitalization	8
Medication Use	27
Oxygen Use	26
Preventive Services	24, 25
Exposures	16-23

C) Respiratory and Environmental Exposure History Questionnaires Administered at 18-22 Months' Corrected Age

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The purpose of this questionnaire is to obtain an **interval** respiratory history and to identify environmental exposures that may increase the likelihood of symptomatic airway dysfunction. Questions are designed to ascertain the frequency and severity of wheezing

and cough episodes and to assess the need for outpatient pulmonary care. In addition, a history of atopy is elicited. There are a total of ~~30~~ 34 questions, encompassing the 27 questions from the discharge and 6 and 12 month questionnaires and 7 concerning infection and allergy history.

This parent interview may also be administered either by telephone prior to the regularly scheduled 18-22 month NICHD developmental follow-up clinic visit or face to face at the time of the visit. Contacting parents prior to the office visit will help improve the Developmental Follow Up Clinic attendance rate. Otherwise, the clinic visit will provide a back up means to contact the family. The 18-22 month interview will be conducted either by the local NICHD Follow Up Program (Option 1) or long distance from Rochester (Option 2), based on center preference (see table 2 below).

5.3 Administration of the ~~Follow-up~~Breathing Outcomes Questionnaires

- The questionnaires are for research only. Caretakers, parents or guardians expressing concern regarding the child's breathing should be encouraged to discuss their concern with the family's primary care physician. Diagnostic or treatment advice should NOT be offered as part of the interview.

5.4 Protocol Violations

The occurrence of any one of the following criteria will determine whether an individual infant will be considered a protocol violation:

- Interview occurring outside the acceptable window (target date + 4 weeks)
- Missed interview

In both of these cases the interview should be conducted at the next available opportunity and should encompass respiratory health since the prior interview.

All protocol violations will be reviewed by the center PI who will discuss each protocol violation with the involved clinicians, identifying steps to avoid future violations.

5.5 Adverse Events

We anticipate no risk to the patient from this observational follow-up study.

Serious adverse events were anticipated in the main SUPPORT Trial for this vulnerable population. Refer to Section 5.5 of the NICHD Neonatal Research Network SUPPORT Trial MOO for more information on adverse event reporting and monitoring.

Chapter 6
NICU Discharge-Baseline Interview

Introduction

The purpose of the discharge questionnaire is to assure adequate randomization of important covariates affecting outpatient respiratory health and to obtain baseline data on home environment and family history of respiratory diseases. There are a total of ~~16~~ 25 questions on the questionnaire; 6 questions on demographics, ~~9~~ 11 questions on home environment and exposures, 2 questions on diet, 1 question on alternate contact information, and a separate ~~5~~6 questions on family history of allergy and respiratory problems.

Each center, regardless of study option chosen, will administer the discharge questionnaire and perform data entry. This will allow ascertainment of baseline data as well as confirming contact information for the family.

Instructions for Completing the NICU Discharge-Baseline Interview (SUPF01)

Timing of the Interview:

This interview should be administered to the parent/guardian by a trained study nurse prior to or within the first 30 days following NICU discharge. If for any reason the infant is enrolled into the Pulmonary Outcome Study later than 30 days following NICU discharge, the questionnaire should be administered prior to interval questionnaires (SUPF02 or SUPF03)

Heading- Infant's Identification
The following information is included in the heading section of all patient specific data forms: Center, Site, Network Number, SUPPORT Follow-up Number, Birth Number and Mother's Initials **(optional).** This information should be completed on the first page of the interview and the SUPPORT Follow-up Number written on subsequent pages in case the completed form pages are separated.

6.1 Conducting the Interview

6.1.1 Initiating the interview:

Script Introducing the Study:
N.B. The interviewer's script is in italics and enclosed in quotations.

"Premature babies are more likely than full term babies to have breathing problems after discharge from the NICU. The purpose of this study is to see whether or not the treatments your baby received as part of the SUPPORT Study improves your baby's breathing in the 18-22 months following the baby's due date.

As part of this study, we will contact you every 6 months or so to ask you questions about your baby's breathing. The questions will be about your baby's breathing symptoms, especially wheezing and coughing, and about your baby's need for medical visits and treatments for breathing problems.

By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical.

We have prepared a ~~diary~~ brochure for you that describes the study and outlines important characteristics of your baby's breathing. ~~to help you keep track of your baby's breathing,~~ especially breathing problems and treatments.

Give ~~diary~~brochure

~~To complete the diary, please record how often your baby has wheezing or coughing, whether your baby visited a doctor's office, emergency room or was hospitalized for breathing problems.~~

When we call, we'd like you to gather ~~the diary and~~ any notes, medications or other information about your baby's breathing. We will ask questions about how often your baby has wheezing or coughing, whether your baby visited a doctor's office, emergency room or was hospitalized for breathing problems, and whether your baby has needed breathing medicines or treatments. If you wish, you may use the brochure to make notes about your baby's breathing.

In order to help us understand your baby's breathing and risk for breathing problems at home, we'd like to ask you a few questions about your home and about whether breathing problems run in the family. As with all information we collect, the answers to these questions will be kept confidential."

Please confirm the study baby's identity.

"We will be discussing, patient name. He/she is a boy/girl born on birth date"
Question 1.
Child's Name:
Please enter the child's name including, nickname that he/she will be called.

Question 2.
Enter the date of the interview in "mm/dd/yyyy" format.

Question 3.
Child's Sex:
Please enter the child's sex.

Question 4.
Child's Birthdate:
Please enter to the child's birth date in "mm/dd/yyyy" format.

Please confirm the identity of the caretaker being interviewed.
Question 5.
"With whom am I speaking?
Question 5a.
What is your relationship to the baby?"

Please specify the primary caretaker's name and relationship to the infant using the relationship codes used in the Network Follow up Program, Appendix B.

Every effort should be made to interview the primary caretaker during this interview and all subsequent interviews (6, 12 and 18 months). If the mother resides in the same household as the child, the mother is the primary caretaker. If each caretaker has exactly 50% custody, record as the primary caretaker, the person who comes in for the discharge. This person should answer all subsequent interviews, if possible.

APPENDIX B OF THE ~~FOLLOW-UP~~BREATHING OUTCOMES MANUAL OF PROCEDURES

RELATIONSHIP CODES

The following codes are used to identify the primary caretaker.
001 - Mother of Child
002 - Father of Child
011 - Husband, Significant Other (SO)(if different from 002)
012 - Wife, Girlfriend (if different from 001)
021 - Maternal grandmother
022 - Paternal (SO) grandmother
031 - Maternal grandfather
032 - Paternal (SO) grandfather
041 - Maternal aunt
042 - Paternal (SO) aunt
051 - Maternal uncle
052 - Paternal (SO) uncle
061 - Brother
062 - Step Brother
071 - Sister
072 - Step Sister
081 - Maternal female cousin
082 - Paternal (SO) female cousin
091 - Maternal male cousin
092 - Paternal (SO) male cousin
101 - Other maternal relative
102 - Other paternal (SO) relative
201 - Foster mother
202 - Foster father
301 - Adoptive mother
302 - Adoptive father
401 - Other non-relative
402 - Social worker/case worker
501 - Staff in congregate care
502 - Still hospitalized
504 - Unknown

Question 6.
Type of Interview:
Record whether the interview conducted face to face or by telephone.

Interview Begins
(N.B. The interviewer's script is in italics and enclosed in quotations)

Script: ***"At this time, we would like a little information about the environment in which your new child will grow up."***

Question 7.
"First, how many people normally live with you in your home for at least 6 months of the year?"
Enter the total number of household members. A household member is a person who spends more than 7 nights in the home over a two week period for at least 6 months of the year.

Question 8.
"After the first few months, will your child be sharing a room with other family members on a regular basis?"
Enter YES if child shares a room with another household member more than 7 nights in a 2 week period.

Question 8a.
If answer to 8 is YES: *"How many people will sleep in the same room with him/her?"*
Please record how many people will sleep in the same room with the child.

Question 9.
"How many rooms are there in your house, excluding closets and bathrooms?" Record how many rooms in the space provided.
A room is a space within the house in which residents play, sleep, work or eat.

Question 10.
"Do you have any pets inside the home?"
If yes record, *"How many dogs in the home? Cats in the home? Do you have other pets in the home? What kinds? How many?"*
If interviewee reports pets, please record the number of dogs and cats separately. Group all other pets together and record total number of pets that are neither a dog nor a cat.

Question 11.
"Does your home or apartment have air conditioning or some kind of cooling?"
Please enter "Yes" or "No"
Question 11.a-11.c_-Please record whether family has air conditioning or evaporative cooling. If family uses another type of home cooling system, please answer YES and record type.

Question 12.
"How is your home heated?, With steam or hot water, with a gas furnace, with electricity, with a wood stove, or something else? "
Please prompt by reading each of the listed heating options. Record all heating methods used in the home or apartment. If more than one heating type is used, please record all heating types used. Steam or hot water heat uses upright radiators or baseboard units. A central gas furnace uses forced air vents that blow air into the room. Included in wood stove heat is use of a fireplace for heat, including fireplaces with energy ~~conserving~~ efficient "inserts".

Question 13.
"What fuel is used most for cooking in your home?"
There is no need to prompt with each alternative cooking fuel. Please record one primary cooking method used in the home or apartment.

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Scripting: "The next questions are about your baby's diet ....."

Question 14.
"Is your child receiving only breast milk, only formula, or both breast milk and formula?"
Record response

Question 14a.
If reply to 14 is only breast milk (choice #1),
"Will the breast milk be supplemented with formula in the next 6 months?"
Please record "Yes", "No" or "Don't Know

Question 14b.
"If so, when do you think the supplement will begin?"
Enter YES, if breast milk will be supplemented with formula. Enter the number of months from date of interview that breast milk will be supplemented with formula.

For interviews conducted after the target period of 30 days following NICU discharge, Question 14 should be stated as, "At the time of NICU discharge was your child receiving" (read all answer choices).

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Scripting: "The next question are about your baby's care environment ....."

Question 15.
"Does the mother plan to work outside the home within the next year?"
Select from responses below.
1. Yes
2. No
3. Don't Know

For interviews conducted after the target period of 30 days following NICU discharge, Question 15 should be stated as, "Does the mother plan to work outside of the home within the first year of the child's life?"

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Scripting: "The next questions are about smoke exposure....."

Question 16.
*"Which one of the following 3 statements best describes the situation regarding smoking in your child's **home?**.....Read all options to the interviewee before recording a response: Smoking is allowed in any common room of the home, smoking is limited to part of the house where the child rarely goes, there is no smoking inside at all?*

Question 16a.
If answer to question 16 is "there is no smoking in the house at all", then ask question 13a, *"Are there any exceptions to this situation?"*

If respondent reports any exceptions, record "Yes". If no, skip to question 17.

Question 16b.
If answer to 16a is "Yes", then ask question16b.
"Under what circumstances are the exceptions allowed?"
Record a brief response as free text.

Question 17.
"*Which one of the following 5 statements best describes the situation regarding smoking in your **car?**.... Read all options to the interviewee before recording a response: Smoking is usually or always allowed, smoking is sometimes allowed, smoking occurs in the car only when the child is not inside, there is no smoking inside the car"*
Record the response as it applies to the main automobile in which the baby rides. If family does not ride in a car (public transportation only or baby doesn't leave home), record response #1.

Questions 17a and 17b. Responses questions to17a and 17b are completed similarly to questions 16a and 16b.

Question 18.
"How often have you smoked since this child was born?"
Please record response, never means never, daily means at least once per day, record occasionally for any quantity between never and daily.

Question 19.
"Altogether, how many people in the child's home smoke?" _____people
Record the number of people who reside in the home (spend more than 7 out of 14 nights in the home) who smoke. Any smoker counts, whether they smoke in the home, outside the home or at some distant location.

Family History Form

Scripting: "In the next section, we'd like to know what breathing and allergy problems run in the family."

Administer the attached Family History Questionnaire using the follow script.

Mother:

"We'll start with the baby's mother. How old is the baby's biologic mother? Does she have bronchitis, emphysema, COPD, bronchiectasis, asthma, inhaled allergies, or food allergies?"
Circle Yes, No, or DK (Don't Know).

"Does she (you) have any other chronic respiratory illnesses?"

"How often do you smoke in the baby's home?"

Father:

"For the baby's biologic father, is he living? How old is he? Does he have bronchitis, emphysema, COPD, bronchiectasis, asthma, inhaled allergies, or food allergies?"

"Does he have any other chronic respiratory illnesses?"
Circle Yes, No, or DK (Don't Know).
"How often does he smoke in the baby's home?"
Complete the remainder of the table by collecting the same medical history using the script above.

Please complete a family history for each of the family relationships listed, mother, father, maternal grandmother (Mom's biologic Mother), maternal grandfather (Mom's biologic Father), paternal grandmother (Dad's biologic Mom), and paternal grandfather (Dad's biologic Father). For each relative above, enter whether they have ever had any of the listed respiratory problems. The interviewer need not explain each diagnosis, but may offer an explanation if asked. Record only those responses that pertain to the baby's biologic relatives. If information is not known by the respondent, record as "DK" (Don't Know).

Question 20.
"Finally, which friend or relative is most likely to be able to contact you 6 months from now in case we lose contact with you?"

Record the information for an alternate contact person who is unlikely to move and the most likely to know the baby's family most recent residence / phone number.

Chapter 7
6 and 12 Month Pulmonary Outcome Questionnaires

Introduction

The purpose of this questionnaire is to obtain an **interval** respiratory history, such that when the 6, 12 and 18-22 month questionnaires are taken together, a complete respiratory history over the time period is collected.

The questionnaire will be administered to the parent or guardian by a certified telephone interviewer at 6 months' CA and again at 12 months' CA.

Centers choosing Option 1 will administer the questionnaire using a certified local interviewer and locally maintained contact information. For centers choosing Option 2, a Rochester Health Services Research Group (RHSRG) certified interviewer will conduct the interview via long distance telephone call using contact information maintained by the local center and faxed or emailed to the RHSRG.

Instructions for Completing the 6 and 12 Month Questionnaire (SUPF02)

Instructions for Completing the NICU Discharge-Baseline Interview (SUPF01)

Timing of the Interview:

This interview should be administered by a certified study interviewer. The target window for this interview is at the following corrected ages: 6 months ± 2 weeks and 12 months ± 2 weeks, with an acceptable window of 6 months ± 1 month and 12 months ± 1 month. If for any reason the infant is enrolled into the Pulmonary Outcome Study later than this time window or becomes available for a Pulmonary Outcomes Interview outside this window, the questionnaire should be administered, collecting an interval history from the time of NICU discharge or the most recent interview, whichever is most recent.

Heading- Infant's Identification
The following information is included in the heading section of all patient specific data forms: Center, Site, Network Number, SUPPORT Follow-up Number, Birth Number and Mother's Initials **(optional).** This information should be completed on the first page of the interview and the SUPPORT Follow-up Number written on subsequent pages in case the completed form pages are separated.

7.1 Conducting the Interview

7.1.1 Initiating the interview:

Please request and confirm the identity of the caretaker who completed the initial interview.

Every effort should be made to interview the primary caretaker who completed the initial interview (hereafter referred to as the primary respondent) during this interview and all subsequent interviews (6, 12 and 18 months). If the mother resides in the same household as the child, the mother is the primary caretaker. If each caretaker has exactly 50% custody,

record as the primary caretaker, the person who comes in for the discharge. This person should answer all interviews, if possible.

The interviewer will need to ask for the primary respondent. In the event that the primary respondent is not available, arrangements should be made to call back at a time when the primary respondent will be free to complete the interview. At least 3 call attempts should be made to reach the primary respondent, after that a secondary respondent, who is familiar with the baby and his or her respiratory health, can be identified to complete the interview.

Introduction Script:
When parent or primary care giver is on phone:

"Hello, my name is <your name>. I am calling from the <NICHD Center>. As you probably remember, when you were in the NICU you enrolled in our study about respiratory health of premature infants. I am calling to ask you some questions about your baby's breathing. It will take about 10-20 minutes to complete. Is this a good time for you?"

"Before we begin this interview, it would be helpful if you could gather ~~the breathing diary given to you when you left the NICU as well as~~ any notes you have about your baby's breathing as well as any medications your child has been prescribed or has been taking and have them in front of you. As with all information we collect, the answers to these questions will be kept confidential."

Question 1.
Please enter date of the interview.

Please confirm the identity and contact information for the study baby to be interviewed.

"We will be discussing, patient name. He/she is a boy/girl born on birth date"
Child's Name:
Please enter the child's name.

Child's Birthdate:
Enter to the child's birth date in "mm/dd/yyyy" format.

Child's Telephone Number:
Enter the telephone number to the child's home.

Child's Address:
Enter the address of the child's home.

Alternate Contact Information
Which friend or relative is most likely to be able to contact you 6 months from now in case we lose contact with you?"

Confirm the contact information for an alternate contact person who is unlikely to move and the most likely to know the baby's family most recent residence / phone number.

Question 2a. and 2b.
Enter name and relationship code of the person being interviewed.
Please specify the primary caretaker's name and relationship to the infant using the relationship codes used in the Network Follow up Program.

Question 3.
Type of interview.
Please specify and record whether the interview was administered face to face or via telephone.

Question 4.
Location of Interview.
Please specify and record whether the interview was administered at the local center (Option 1) or by the Rochester site (Option 2).

Instructions:
Parents or guardians expressing concerns regarding their child's breathing should be advised to discuss them with the family's primary care physician.

Where the phrase "last contact" is used below, please substitute with the most specific relevant time prompt, e.g. for the 6 month interview, refer to "since NICU discharge"; for the 12 month interview, refer to "over the past 6 months", etc.

Interview begins:
(N.B. The interviewer's script is in italics and enclosed in quotations)

Scripting:
"Some of these questions will be familiar to you. Since we last spoke (__ __) months ago on (__ __/__ __/__ __) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing problems your child may have....."

Question 5.
"Has the child been with you during the past 6 months?"
Please enter "Yes" or "No". If child has been with the interviewee less than 6 months, please enter "No".

Scripting: "Since <our last contact> with you about your child....."
Please replace the phrase "our last contact", with an interview specific prompt, e.g. "since discharge from the NICU" at the 6 month interview or "since our telephone conversation 6 months ago", for the 12 and 18 month interviews. Equivalent phrases may be used.

Question 6.
"How many times has your child visited a doctor's office?" |___|___| times
Record the number of times that the baby visited the doctor's office for any reason.

Question 6a.

"How many of these times were because of wheezing or breathing problems?"
Record the number of times that the baby visited the doctor's office with breathing problems as one of the 2 major concerns for the visit.

Scripting: "Since <our last contact> with you about your child....."
Please replace the phrase "our last contact", with an interview specific prompt, e.g. "since discharge from the NICU" at the 6 month interview or "since our telephone conversation 6 months ago", for the 12 and 18 month interviews. Equivalent phrases may be used.

Question 7.
"How many times has your child visited an Emergency Department (Emergency room)?"
|___|___| times
Record the number of times that the baby visited the emergency department or emergency room for any reason.

Question 7a.
"*How many of these times were because of wheezing or breathing problems?*"
Record the number of times that the baby visited emergency services with breathing problems as one of the 2 major concerns for the visit.

Question 8.
"How many times has your child stayed in the hospital for 1 or more nights in a row?"
|___|___| times
Record the number of times the baby was hospitalized for any reason, i.e the number of hospitalizations, not the number of hospitalized days.

Question 8a.
"How many of these times were because of wheezing or breathing problems?" |___|___| times
Record the number of times that the baby was hospitalized with breathing problems as one of the 2 major concerns for the visit.

Script:

"The next questions are about your baby's breathing. .....

The first question is about wheezing. By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical."

Question 9.
"Since <our last contact> with you, has your baby's chest sounded wheezy or whistling?"
Enter yes if the respondent reports that the baby's chest has sounded wheezy or whistling. The interviewer may repeat the verbal and audio descriptions of wheezing may be repeated to the respondent. If respondent answers "I don't know", interviewer should ask respondent to think

back over the time period, repeating the description. If parent is still not sure, record "don't know".

Question 9a.

"Has your baby's breathing sounded like this?" ***(play audio clip of wheezing).***

This question is intended for all respondents, regardless of whether they reported wheezing in question 9. The audio clip is from a patient with severe, audible wheezing and represents only one of many manifestation of wheezing breathing sounds. If asked, the interviewer may say that this represents just one type of wheezing. We wish to know about all wheezing and therefore we asked two questions.

Record response, "Yes" or "No". If respondent replies "no" or "don't know", interview skips to question 10. If yes, proceed to questions 9b-g.

Question 9b.

"Has this occurred with colds?"

A "cold" is an upper respiratory infection; other phrases for a "cold" include, "head cold", "rhinitis, "runny or water nose" or "sniffles". A cold may be complicated by an otitis media (ear infection).

A "cold" does not include "chest cold", "bronchitis", "pneumonia", or "bronchiolitis".

Question 9c.

"Has your child's chest sounded wheezy or whistling apart from colds?"

Enter "yes" if the baby had wheezy or whistling in the chest at a time when he / she did not have a cold.

Question 9d.

"During what month did your child's chest first sound wheezy or whistling?"

_____ month ____ year

Please record the month and year during which the child's chest first sounded wheezy or whistling. The respondent may indicate the child's age at which the child's chest first sounded wheezy or whistling. The interviewer should record the month and year of the event.

Here the month and year, rather than the age, that the symptoms began is recorded in an effort to avoid confusion regarding chronologic and corrected ages.

The next 4 questions use similar phrases and the same response options. Please emphasize the phrases which are unique in each question ("on average" or "worst two week period", "daytime" or "nighttime"). If the respondent gives the same response to 5e as 5f, please confirm with the respondent that 5e refers to "on average" and that 5f refers to the "worst two week period".

Question 9e1.

*"~~Over the past 6 months~~Since our last contact with you, **on average**, how often has your child's chest sounded wheezy or whistling during the daytime? Would you say never, twice a week, more than 2 times a week, but not every day, every day, but not all the time, everyday, all the time."*

Record response. Interviewer may repeat the choices or help respondent settle upon the choice.

Question 9e2.

*"~~Over the past 6 months~~Since our last contact with you, **on average**, how often has your child's chest sounded wheezy or whistling during the nighttime? Would you say never, twice a week, more than 2 times a week, but not every day, every day, but not all the time, everyday, all the time."*

Record response. Interviewer may repeat the choices or help respondent settle upon the choice.

Question 9f1.

*"Since our last contact with you~~Over the past 6 months~~, **during the worst 2 week period,** how often has your child's chest sounded wheezy or whistling during the daytime? Would you say never, twice a week, more than 2 times a week, but not every day, every day, but not all the time, everyday, all the time."*

Record response. Interviewer may repeat the choices or help respondent settle upon the choice.

Question 9f2.

*"Since our last contact with you~~Over the past 6 months~~, **during the worst 2 week period,** how often has your child's chest sounded wheezy or whistling during the nighttime? Would you say never, twice a week, more than 2 times a week, but not every day, every day, but not all the time, everyday, all the time."*

Record response. Interviewer may repeat the choices or help respondent settle upon the choice.

Question 9g.

"Since our last contact with you, has your child ~~taken any medicine prescribed~~been diagnosed with wheezing ~~for wheezing~~?"

Record "Yes" or "No". Physician diagnosed wheezing, wheezy or whistling breath sounds should be recorded as a "Yes" response.

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Question 10.

"Since our last contact with you, has your child had a cough for 3 or more days when he/she did not have a cold?"

Record whether the baby coughs for more than 3 days when otherwise well. Do not include coughing associated with eating, drinking or choking. See question 9 for clarification of phrase "cold".

Question 10a.

"At what time of the day has this cough usually occurred? In the morning; shortly after rising; later in the day; during the night; no relation to time of day?"

Interviewer should read all responses to the respondent and circle all that apply.

Question 10b.

"Has he/she coughed on most days for as much as 2 to 3 months?"

Please record "Yes" or "No"

Question 10c.

"During what month did your child first develop the cough?"

Record month and year that the cough first developed, when the respondent recognized the cough whether or not they view it as a problem.

Question 10d.

"Has your child's chest ever sounded wheezy or whistling with episodes of coughing?"

Record yes if the respondent associates wheezing or whistling breath sounds with the presence of the cough.

Questions 10e1-10f2. Questions 10e1-10f2 are completed similarly to questions 9e1-9f2.

Question 11.

*"~~Over the past 6 months,~~ Since our last contact with you, **on average**, how many **days per month** did you have to change your daytime or evening plans because of your child's breathing problems: Was it…*

None, we never had to change plans

More than none, but less than 3 days,

3 to 6 days or

7 or more days."

Please read the choices to the respondent and record their response. The question is designed to determine the number of days that the respondent reports having to change plans because the baby's breathing is different from baseline. An example of a changed plan includes withholding the baby from a planned daycare or babysitting situation because he / she is wheezing.

This does not include preventive avoidance, such as avoiding social situations or trips because the baby might get sick or may be exposed to another child. The interviewer may assist the respondent in selecting ~~a number by establishing a~~ a response by repeating the choices ~~range~~, then having the respondent select a specific answer.

Question 12.

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"Since our last contact with you, ~~Over the past 6 months,~~ ***during the worst 2 week period****, how many* ***days*** *did you have to change ~~for~~ your daytime or evening plans because of your child's breathing problems: Was it…*

None, we never had to change plans
More than none but less than 3 days,
3 to 6 days or
7 or more days."

~~"|__|__|__| # of days~~

———Interviewer should emphasize the "worst 2 week period". Record response using criteria similar to those in Question 11.

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The next 4 questions relate to respiratory diagnoses that may be associated with wheezing and airway dysfunction, either directly, as secondary symptom or as a condition that may be confused with airway dysfunction.

Question 13.
"Since our last contact with you, has your child had asthma, ~~or~~ reactive airways disease or a BPD flare-up diagnosed by a doctor?"
Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 14.
"Since our last contact with you, has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?"
Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 15.
"Since our last contact with you, has your child had croup diagnosed by a doctor?"
Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Script: "The next question are about your baby's diet……"

Question 16.
"In the past 6 months, did your baby receive mother's breast milk, either at breast, from a bottle or through a tube?"
If baby received any breast milk, record "Yes".

If yes to Question 16, answer question 16a and 16b, if "No", skip to Question 17:

Question 16a.
"For how many months did your child receive breast milk? Would you say? ….Less than 1 month, 1-3 months, 4-6 months?"
Record duration of time that the baby received any breast milk.

Question 16b.

"For how many months did your child receive breast milk for more than half of his/her feedings? Would you say… Less than 1 month, 1-3 months, 4-6 months?"

Record duration of time that the baby received more than ½ of feedings from breast milk, provided by any route.

A mother who fed her infant breast milk 25% of the time and formula 75% of the time, weaning the baby at 4 months, would answer "yes" to question 16, "4-6 months" to question 16a, and "less than 1 month" to question 16b.

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Script: "***The next questions are about smoke exposure……"***

Question 17.
*"Which of the following 3 statements best describes the situation regarding smoking in your child's **home?**…… Read all options to the interviewee before recording a response: Smoking is allowed in any common room of the home, smoking is limited to part of the house where the child rarely goes, there is no smoking inside at all?"*

Question 17a.
If answer to question 17 is "there is no smoking inside at all", then ask question 17a,
"Are there any exceptions to this situation?"
If respondent reports any exceptions, record "Yes". If no, skip to question 18.

Question 17b.
If answer to 17a is "Yes", then ask question17b.
"Under what circumstances are the exceptions allowed?"
Record a brief response as free text.

Question 18.
*"Which of the following 5 statements best describes the situation regarding smoking in your **car?**…. Read all options to the interviewee before recording a response: Smoking is usually or always allowed, smoking is sometimes allowed, smoking occurs in the car only when the child is not inside, there is no smoking inside the car"*
Record the response as it applies to the main automobile in which the baby rides. If family does not ride in a car (public transportation only or baby doesn't leave home), record response #1.

Question 18a and 18b. Responses questions to 18a and 18b are completed similarly to questions 17a and 17b.

Question 19.
'How often has the mother or primary caregiver smoked since your child was born?'
If speaking with the mother, please substitute "you" for "mother or primary caregiver". Record response based on occurrence of any smoking activity, regardless of where it takes place. Record "Never" if the mother or primary care giver has never smoked

anywhere since the baby was born, record "Daily" if she /he smokes daily in any location, and record "Occasionally" if response is neither "Never" nor "Daily".

Question 20.
"How many people in the child's home smoke?" |___|___| people
Record response based on occurrence of any smoking activity, regardless of where it takes place.

Script: *"The next questions are about your home and your babysitter's home or day care"*

Question 21.
"Approximately how many hours per week does your child spend at a babysitter's home or day care?" |___|___| hrs If 0 skip to question 22.
Record the number of hours that the baby spends outside his/her home, regardless of whether this is in the home of another parent, grandparent, or friend.

Question 21a.
If response to question 21 is greater than 0,
"How frequent is there smoke exposure at the babysitter or daycare?"
Record response based on occurrence of any smoking activity, regardless of where it takes place. Record never if there is no smoking allowed inside the babysitter or daycare provider's edifice in any location, record daily if smoking occurs inside the edifice daily in any location, and record occasionally if response is neither never nor daily.

Question 21b.
"How many children beside your baby are in the daycare?"
Record the average number of children less than 12 years of age who inhabited the babysitter or daycare over the past 2 weeks when the baby was present.

Question 22.
"How many children under 12 live in your house?" |___|___| children
Record number of children who spend more than 7 nights in the home over a two week period.

Question 23.
"Do you have any pets inside the home?"
Record "Yes" or "No"

Question 23a. If yes record,
"How many dogs? Cats? Do you have other pets? What kinds? How many?"

If respondent reports pets, please record the number of dogs and cats separately. Group all other pets together and record total number of pets that are neither a dog nor a cat.

Script: "*The last questions involve respiratory treatments that your baby may receive.....*"

Question 24.
"Has your child had RSV shots (palivizumab) to prevent Respiratory Syncytial Virus (Synagis, palivizumab, RSV shot)?"

Record respondent's answer, "Yes", "No" or "Don't know". If respondent does not recognize the treatment, record "Don't Know".

Question 25.
"Has your child had a flu shot?"

Record respondent's answer, "Yes", "No" or "Don't know". If respondent does not recognize the vaccine, record "Don't Know".

Question 26.
"Is your child on any oxygen therapy at home?"

Record respondent's answer, "Yes" or "No". If respondent does not know, the interviewer should prompt further by asking, "does your baby use any oxygen equipment, such as an oxygen tank, at home?"

Question 26a – 26c.
These questions can be answered using the following script.

If response to question 26 is "Yes",
"What device is used to provide the oxygen?.....Oxygen hood, nasal cannula or ventilator?"

Record response in checkbox provided.

If response to question 26 is "Yes", the interviewer should ask,
"*What percent oxygen does your baby use?"*

Record response as fraction inspired oxygen (FiO2) in the space adjacent to the oxygen delivery device. For example, room air (ambient air) is 21% oxygen, enter as FiO2 value of 0.21; pure oxygen is 100%, enter as FIO2 value of 1.0

If response to question 26 is either "nasal cannula" or "oxygen hood", interviewer asks,
"How many liters of oxygen does the baby receive?"

Record value as liters per minute (1cc is .001liters, 1/8 liter is 0.125 liters, ¼ liter is 0.25 liters, etc.)

MEDICATIONS

Script: *"The last two questions involve the medicines your child is taking for breathing problems....."*

Question 27.
"Since our last contact with you, w~~W~~hat medicines has your baby taken ~~over the past 6 months~~, including medicines delivered by a nebulizer or breathing machine?"

For this question, record all respiratory related medications. Record a written response in the table and later, after the interview, record the medication code from the table

below. Medications that do not appear on the list are unlikely to be used to treat respiratory conditions in this age group. Do not prompt for each medication in the medication list.

Chapter 8
18-22 Month Questionnaire

Introduction

The purpose of this questionnaire is to obtain an **interval** respiratory history and to identify a history of atopy that may increase the likelihood of symptomatic airway dysfunction. Questions are designed to ascertain the frequency and severity of wheezing and cough episodes and to assess the need for outpatient pulmonary care. In addition, risk factors obtained at the 1st interview will be confirmed. There are a total of ~~30~~ 34 questions, encompassing 27 questions from the ~~discharge, 6~~ month and 12 month questionnaires and 7 questions concerning respiratory infections and allergies.

This interview will be conducted at 18-22 months' corrected age, either by the local NICHD Follow Up Program (Option 1) or long distance from Rochester (Option 2), based on center preference.

Instructions for Completing the 18-22 Month Questionnaire (SUPF03)
Timing of the Interview:
The target window for this interview is between 18 and 22 months' corrected age. If for any reason the infant is enrolled into the Pulmonary Outcome Study at this time window or becomes available for a Pulmonary Outcomes Interview outside this window, the questionnaire should be administered, collecting an interval history from the time of NICU discharge or the most recent interview, whichever is most recent.

This interview should be administered by a certified study interviewer either by telephone prior to the regularly scheduled 18-22 month NICHD developmental follow-up clinic visit or face to face at the time of the visit.

Heading- Infant's Identification
The following information is included in the heading section of all patient specific data forms: Center, Site, Network Number, SUPPORT Follow-up Number, Birth Number and Mother's Initials **(optional).** This information should be completed on the first page of the interview and the SUPPORT Follow-up Number written on subsequent pages in case the completed form pages are separated.

8.1 Conducting the Interview

8.1.1 Initiating the interview:

The 18-22 month questionnaire is conducted in the same fashion as for the 6 and 12 month interviews. In addition to the 27 questions included in the 6 and 12 month questionnaires, the 18-22 month questionnaire includes 7 questions about allergies.

See Chapter 8 of the manual of procedures for directions to administer questions 1-~~28~~ 27 of the 18-22 month questionnaire. Directions for questions 28-34 begin here.

Script: "*The ~~last~~ next 2 questions regard ~~allergies~~ about respiratory infections.....*"

Question 28.
*"**During the past year**, for how many days has your child been unable to do his/her usual activities because of illnesses such as chest (not head) colds, bronchitis, asthma or pneumonia? 0-3 per year, 4-5 per year, 6-9 per year, more than 9 per year?"*

Question 29.
*"**During the past year**, ~~H~~how many head colds (common colds) **~~per year does~~has** your child ~~usually have~~had? Would you say...0-3 per year, 4-5 per year, 6-9 per year, more than 9 per year?"*

Script: "*The last questions regard allergies.....*"

Question 30.
*"Has your child **ever** had hay fever or any other condition that makes his/her nose runny, stuffy, or itchy **apart** from colds?"*
Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 31.
*"Has your child **ever** had allergies which cause nose, eye or lung problems?"*
Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 32.
*"Has your child **ever** been allergic to any food?"*
Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 33.
*"Has he/she **ever** been allergic to any medicine?"*
Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 34.
*"Has your child **ever** had eczema (allergic skin rash)?"*
Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 34a.
If Question 34 is "Yes",
"Was this diagnosed by a doctor?"
Record response, "Yes" or "No"

APPENDIX A
List of Acronyms

BOOST Trial – Benefits of Oxygen Saturation Targeting
BPD – Bronchopulmonary Dysplasia
CA – Corrected Age
CLD – Chronic Lung Disease
CPAP – Positive pressure applied with a face mask to help keep lungs inflated
FEF – Forced Expiratory Flow
GA – Gestational Age
GDB – Generic Data Base for the NICHD Neonatal Research Network
HDMA – House Dust Mite Allergen
HIPPA – Health Insurance Portability and Accountability Act of 1996
HSR Group – University of Rochester Health Services Research Group
IRB – Institutional Review Board
LBW – Low Birth Weight
NBW – Normal Birth Weight
NHLBI Consensus Expert Report -
NICHD – The National Institute of Child Health and Human Development
NICU – Neonatal Intensive Care Unit
PFT – Pulmonary Function Testing
RDS – Respiratory Distress Syndrome
ROP – Retinopathy of Prematurity
RSV - Respiratory Syncytial Virus
SUPPORT Trial– The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants
UKOS – The United Kingdom Oscillator Study
VLBW – Very Low Birth Weight

APPENDIX B
~~FOLLOW-UP~~BREATHING OUTCOMES STUDY FORMS

SUPF01 **NICU Discharge-Baseline Interview**

SUPF02 **6 Month Interview and 12 Month Interview**

SUPF03 **18-22 Month Interview**

Insert Forms

APPENDIX C

Appendix E - Revised 9-1-05

SAMPLE CONSENT FORMS

SAMPLE CONSENT FORM FOR PATIENTS ENROLLED IN SUPPORT

TITLE: SUPPORT Trial ~~Pulmonary~~ Breathing Outcomes Study- Follow-up Study of Infants Enrolled in the NICHD Neonatal Research Network SUPPORT Trial

PRINCIPAL INVESTIGATOR: Timothy P. Stevens, MD MPH

CO-PRINCIPAL INVESTIGATOR: Dale L. Phelps, MD

INTRODUCTION and BACKGROUND:
This consent form describes a research study and what you may expect if you decide to have your infant participate. You are encouraged to read this consent form carefully and to ask the person who presents it any questions you may have before making your decision whether or not to have your infant participate.

This form describes the known possible risks and benefits in the study. You are completely free to choose whether to participate.

Your infant is invited to be a part of this research project because (s)he is a premature baby who is a member of the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network SUPPORT Trial. As described in the SUPPORT Trial Consent that was discussed with you previously, the SUPPORT Trial is designed to find out more about treatment with CPAP (positive pressure applied with a face mask to help keep the lungs inflated) and learn the appropriate levels of oxygen saturation (oxygen levels in the blood) in premature babies. The SUPPORT Study will determine the effect of these treatments on your baby's respiratory and visual health prior to discharge from the Neonatal Intensive Care Unit (NICU).

However, we know that many babies born as early as your baby are at risk for breathing problems, especially wheezing and coughing during early childhood, after discharge from the NICU.

PURPOSE:
The purpose of Pulmonary Outcomes Study described here is to determine the effect of the SUPPORT Study treatment on your baby's respiratory health in early childhood, during the first 18-22 months after his/her expected delivery at full term.

PROCEDURES:
You and your infant's participation will begin with an interview before your infant is discharged from the hospital or at the time of your regular follow-up visit with the NICU Outpatient Clinic. At this interview we will ask you questions about your family, including questions about family history of breathing problems, and questions about your home, including things that may

increase your child's risk of breathing problems. You do not need to answer any questions that make you uncomfortable. The interview will take about 15 minutes.

We will continue to stay in touch with you and your infant by telephone or in person at one of your visits **((((Customize language here based on which option your center chose for administering the questionnaires))))** every 6 months over the next 18-22 months, a total of three times. At these times, we will ask questions about your child's breathing (especially wheezing and coughing), medication use, and visits to a Doctor, Emergency Room, or Hospital visits for treatment of breathing problems. We will also ask you several questions about your family and yourself. The entire call should take about 15 minutes of your time, less if your baby has had no breathing problems.

We will schedule the telephone calls at a time that is convenient for you. The telephone calls will occur when your infant is 6, 12, and 18 months after his/her expected delivery at full term.

The results from your baby's questionnaire will be combined with other infants from around the country. However, your baby's name will not be used.

We also ask your permission to contact your baby's Doctor to obtain their assessment of your baby's breathing and need for breathing treatments.

NUMBER OF PARTICIPANTS:
All babies who participate in the SUPPORT Trial will be offered the opportunity to participate in this study. There will be close to 1300 infants enrolled in the SUPPORT Trial. We hope that as many as possible will choose to participate in this study to help determine the long-term effect of the SUPPORT Study treatments. Approximately 40 babies will be enrolled locally.

RISKS AND DISCOMFORTS:
You may experience anxiety or psychological discomfort while completing these questionnaires and/or the interviews. You are free to choose not to answer any question for any reason.

BENEFITS:
The major benefit to you and your infant is that actual or potential breathing problems experienced by your baby could be identified early and brought to the attention of your baby's Doctor for treatment.

CONFIDENTIALITY OF RECORDS AND HIPAA AUTHORIZATION
While we will make every effort to keep information we learn about you private, this cannot be guaranteed. Other people may need to see the information. While they normally protect the privacy of the information, they may not be required to do so by law. Results of the research may be presented at meetings or in publications, but your name will never be used.

~~The federal Health Insurance Portability and Accountability Act (HIPAA) requires us to get your permission to use health information about you that we either create or use as part of the research. This permission is called an Authorization. We will use your child's research record, related information from your child's medical records, results of laboratory and other diagnostic tests obtained during his/her initial hospitalization, as well as the information and test results obtained during the telephone interviews of your baby's breathing.~~

We will use your child's health information to conduct the study, to monitor your child's respiratory status and to determine long term effects on breathing of the SUPPORT Study treatments. Health information is used to report results of research to sponsors and federal regulators. It may be audited to make sure we are following regulations, policies and study plans. If you have never received a copy of the Strong Health HIPAA Notice, please ask the investigator for one. To meet regulations or for reasons related to this research, the study investigator may share a copy of this consent form and records that identify you with the following people: The Department of Health and Human Services, the University of Rochester, the NICHD Neonatal Research Network and organizations (like RTI International) used by NICHD to manage studies.

If you decide to have your child take part, your Authorization for this study will not expire unless you cancel or revoke it. You can always cancel this Authorization by writing to the study investigator. If you cancel your Authorization, your child will be removed from the study. However, standard medical care and any other benefits to which you are otherwise entitled will not be affected. Canceling your Authorization only affects uses and sharing of information after the study investigator gets your written request. Information gathered before then may need to be used and given to others. For example, information gathered during your child's initial hospitalization will be sent to the NICHD Neonatal Research Network and to RTI International.

As stated in the section on Voluntary Participation below, you can also refuse to sign this consent/Authorization and not be part of the study. You can also tell us you want to leave the study at any time without canceling the Authorization. By signing this consent form, you give us permission to use and/or share your health information.

COSTS:
There is no cost to you to participate in the study.

CONTACT PERSONS:
For more information about this research, or if you believe your infant has suffered a research-related injury, please contact Timothy P. Stevens, MD MPH or Dale L. Phelps, MD (Principal Investigators) at (585) 275-2972. You can also reach them, or one of the other attending physicians, by asking the unit secretary in the NICU to page them.

If you have any questions about your rights as a research subject, you may contact the Human Subjects Protection Specialist at the University of Rochester Research Subjects Review Board at Box 315, 601 Elmwood Avenue, Rochester, NY 14642-8315. Telephone: (585) 276-0005, for long-distance you may call toll-free, (877) 449-4441.

VOLUNTARY PARTICIPATION:
Taking part in this study is entirely voluntary. You are free not to participate or to withdraw at any time, for whatever reason, without risking loss of present or future care you would otherwise expect to receive. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

SIGNATURES/ DATES:

I have read (or have had read to me) the contents of this permission form and have been

encouraged to ask questions. I have received answers to my questions. I give permission for my child to participate in this study. I will receive a signed copy of this form for my records and future reference.

_____
Study Subject (Print)

_____	_____	_____
Parent/Guardian Signature	Print Name	Date

PERSON OBTAINING CONSENT

I have read this form to the parent/guardian of this subject and/or the parent/guardian of this subject has read this form. An explanation of the research was given and questions from the subject's family were solicited and answered to their satisfaction. In my judgment, the parent/guardian has demonstrated comprehension of the information. I will provide the parent/guardian with signed copy of this consent form.

_____	_____	_____
Signature, person conducting Informed Consent	Print Name	Date

SAMPLE CONSENT FORM FOR FUTURE SUPPORT PATIENTS

Consent to Act as a Research Subject

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial of the NICHD Neonatal Research Network

Neil Finer, MD, his associates, and the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network are conducting a research study to find out more about treatment with CPAP (positive pressure applied with a face mask to help keep the lungs inflated) and learn the appropriate levels of oxygen saturation (oxygen levels in the blood) in premature babies. You are being asked to allow your child to be in the study because there is a possibility he/she will be born between 16 and 12 weeks early (24-28 weeks gestational age).

The purposes of this trial are the following:
1) To compare infants who receive delivery room CPAP and who have strict guidelines for having a breathing tube placed with infants who have the tube placed and surfactant (a liquid which helps babies with immature lungs breath easier by helping keep their lungs from collapsing) given in the delivery room.
2) To compare low range (85-89%) oxygen saturation levels with high range (91-95%) levels to determine if a lower range results in decreased ROP (Retinopathy of Prematurity, an eye disease that may result in impairment of vision or even blindness, which may be caused by excessive levels of oxygen.)

Duration of the Study: We expect to include about 1300 babies in the study from all the NICHD Neonatal Research Network hospitals over a two-year period.

The use of CPAP and Intubation/Surfactant are both treatments currently used in the delivery room at UCSD. The decision as to which to use is currently made by the physician attending the delivery.

The oxygen level currently used in the NICU at UCSD is between 85% and 95%. Both treatment groups (85-89% and 91-95%) fall within that range. The study will attempt to keep babies in one of these two smaller ranges.

If you agree to allow your child to be in this study, the following will happen to your child: Prior to delivery, and after your permission, your baby will be randomized (chosen by chance like the flip of a coin) to one of two lung treatment strategies. The treatments are as follows:
1) CPAP in the delivery room immediately after birth and continuing in the NICU, or
2) The placement of a tube in his/her trachea (windpipe) in the delivery room followed by surfactant administration and ventilation (breathing for the baby using a machine).

In addition to being randomly assigned to one of the two groups described above, your baby will be randomized to a High reading or Low reading oximeter (a monitor that displays how

much oxygen is in the blood). The oximeters (oxygen monitors) used in this trial are FDA approved oximeters which have been modified for research purposes. This modification makes the monitors show a value which is either slightly higher or slightly lower than the true oxygen level when values are between 85 and 95%. Outside those ranges, the oximeter works the same as the standard of care device.

Which group your baby is randomized to will not be known to the nurse taking care of your baby, or his/her physician. Only the study coordinator will know which group your baby is in. Within the range of oxygen which we normally keep babies in, your baby will either be on the high end of normal or the low end of normal. He/she will remain on this device until he/she reaches 36 weeks adjusted age. (e. g. 24 wks gestation plus 12 weeks of age = 36 weeks adjusted age). Other care will be conducted as normal during his/her participation in the study.

We will continue to stay in touch with you and your infant by telephone or in person at one of your visits ((((Customize language here based on which option your center chose for administering the questionnaires)))) every 6 months over the next 18-22 months, a total of three times. At these times, we will ask questions about your child's breathing (especially wheezing and coughing), medication use, and visits to a Doctor, Emergency Room, or Hospital for treatment of breathing problems. We will also ask you several questions about your family and yourself. The entire call should take about 15 minutes of your time, less if your baby has had no breathing problems.

We will schedule the telephone calls at a time that is convenient for you. The telephone calls will occur when your infant is 6, 12, and 18 months after his/her expected delivery at full term.

The results from your baby's questionnaire will be combined with other infants from around the country. However, your baby's name will not be used.

Participation in this study may involve some added risks or discomforts. Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby. Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted ventilation (methods to help them breathe). If the attending physician deems this necessary, participation in the study will not affect this decision. Some unknown risks may be learned during the study. If these occur, you will be informed by the study personnel. The only other risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential. There will be no name or other patient identification in any study report that may be published after the study is completed. Measures taken to protect you and your baby's identity are described in the confidentiality section of this document.

There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen near discharge) **or wheezing** <u>or cough</u> **in the first 2 years** and/or a decrease in the need for eye surgery as a result of exposure to oxygen. Because we do not know in advance the actual strategies chosen for your child, or which of the treatment strategies is the most effective, it is also possible that your baby will receive no direct benefit. The knowledge learned from this study may help us treat babies in the future. However, as noted above, each of the 4 possible combinations of treatments is considered by some units to represent their desired approach.

If your child is injured as a direct result of participation in this research, the University of California will provide any medical care your child needs to treat those injuries. The University will not provide any other form of compensation to you if your child is injured. You may call the UCSD Human Research Protections Program office at (858) 455-5050 for more information about this, or to inquire about your rights as a research subject, or to report research-related problems.

_____ has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Wade Rich, the Study Coordinator, or Renee Bridge, the Research Nurse, at 619-543-6560. You may contact the principal investigator Dr. Neil Finer at 619-543-3794

As an alternative to participation in this study you may decide to have your baby's doctor decide which treatment your baby will receive. If you decide not to include your child in this study, none of his/her medical information will be included in the study data. Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care your child will receive at this institution of other loss of benefits to which your child is entitled. If you withdraw your child from the study, the attending physician will decide whether to maintain current treatment or change it, based on your child's needs at the time of the decision. Data collection for research purposes will stop at that time.

Clinical information will be collected from your baby's chart by study personnel at UCSD. Information will be labeled with a code number. Coded information will be sent to the NICHD Neonatal Network's Data Coordinating Center at RTI International in Research Triangle Park, North Carolina. The study log linking the code number with your baby's identity will be kept under lock and key at UCSD. Information directly identifying your baby will not leave UCSD. Research records will be kept confidential to the extent provided by law.

You may withdraw your child from the study for any reason. In addition, the study doctors may decide to withdraw your child if they feel it is in his/her best interest to do so. You have received a copy of this consent document to keep and the Experimental Subject's Bill of Rights.

You agree to have your child participate.

_____
Parent's or legal guardian's signature DATE

_____
Relationship of legal guardian to subject DATE

_____
Signature of person explaining and getting consent DATE

APPENDIX D
RELATIONSHIP CODES

The following codes are used to identify the primary caretaker.
001 - Mother of Child
002 - Father of Child
011 - Husband, Significant Other (SO)(if different from 002)
012 - Wife, Girlfriend (if different from 001)
021 - Maternal grandmother
022 - Paternal (SO) grandmother
031 - Maternal grandfather
032 - Paternal (SO) grandfather
041 - Maternal aunt
042 - Paternal (SO) aunt
051 - Maternal uncle
052 - Paternal (SO) uncle
061 - Brother
062 - Step Brother
071 - Sister
072 - Step Sister
081 - Maternal female cousin
082 - Paternal (SO) female cousin
091 - Maternal male cousin
092 - Paternal (SO) male cousin
101 - Other maternal relative
102 - Other paternal (SO) relative
201 - Foster mother
202 - Foster father
301 - Adoptive mother
302 - Adoptive father
401 - Other non-relative
402 - Social worker/case worker
501 - Staff in congregate care
502 - Still hospitalized
504 - Unknown

APPENDIX E
BREATHING BROCHUREEATHING DIARY

To be distributed by email

APPENDIX F
CONTACT INFORMATION TEMPLATE

All centers (Option 1 and 2 centers) will track their own patient's telephone and contact information for the purpose of administering telephone questionnaires at 6, 12 and 18-22 months.

The following core set of contact information is recommended for all enrolled patients.

For option 2 centers, use template to fax or email patient contact information to the Rochester site.

Network number: _____

Patient Name: First _____ Last: _____

Nickname: *(If relevant)* _____

DOB: __ __ / __ __ / __ __ __ __

Gender: Male Female

Name of Prior Interview Respondent (Primary Respondent)

Primary Respondent Contact Information

Name: _____

Relationship to patient: _____

Mailing address: _____

_____

_____

Telephone number #1: _____

Telephone number #2: _____

Email: _____

Secondary (Backup) Caretaker Information

Name: _____

Relationship to patient: _____

Mailing address: _____

_____

_____

Telephone number #1: _____

Telephone number #2: _____

Email: _____

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; wrich@ucsd.edu; nfiner@ucsd.edu
Subject: RE: SUPPORT visits by Dr.Sayre
Date: Thursday, November 03, 2005 9:16:14 AM

I think Wade's memo, with the corrections suggested by Rose, is fine.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, November 03, 2005 9:13 AM
To: wrich@ucsd.edu; nfiner@ucsd.edu; Das, Abhik
Subject: Re: SUPPORT visits by Dr.Sayre

Change the last sentence to
"Data and patient information with respect to the SUPPORT trial are to
be treated as CONFIDENTIAL and should not be communicated with Masimo
company personnel."

Also, wait to hear from Abhik also on this one.

Thanks for your attention to this!!
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wade Rich <wrich@ucsd.edu>
To: nfiner@ucsd.edu <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD)
<higginsr@mail.nih.gov>
Sent: Thu Nov 03 09:08:36 2005
Subject: FW: SUPPORT visits by Dr.Sayre

Rose, Neil,

I was going to send this to sites and Maribeth. Can you review? Thanks.

Coordinators at more than one site have asked me why we have
scheduled visits from Maribeth Sayre at Masimo for Support centers.
Please be advised that
these visits are being planned, carried out, and paid for by Masimo.
The are not related to the study in any way. If you need help with your
oximeters, you may
call Maribeth as you always have and she will assist you as best she
can. You may treat any visits initiated by Masimo as a sales call, and
treat them as you would any other visit from a company representative.
You should not, at the request of Dr. Higgins, discuss patient
information or study data with Dr. Sayre.

Thank you,
Wade Rich

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 02, 2005 9:42 PM
To: 'Higgins, Rosemary (NIH/NICHD)'
Cc: 'wade'
Subject: RE: SUPPORT visits by Dr.Sayre

Hi Rose

I have no knowledge of this and there should not be any Masimo visits for SUPPORT. The equipment is bought and paid for, this is not an FDA trial, and they have no role at the sites. In addition I do not want them interfering with the study oximeters. I will ask Wade to call Maribeth and Masimo and clarify.

I am out of town for the next 8 days, but I will try to stay tuned to my email. I'm not sure if I will be able to do this. If necessary I will call her myself.

Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 02, 2005 12:03 PM
To: Nancy Peters
Cc: nfiner@ucsd.edu; moshea@wfubmc.edu; Das, Abhik
Subject: RE: SUPPORT visits by Dr.Sayre

Hi Nancy,

It is my understanding that Dr. Sayre is with Massimo, correct? If so, she should discuss only the equipment. No patient information or study data can be shared with her.

Thanks for asking!
Rose

From: Nancy Peters [mailto:npeters@wfubmc.edu]
Sent: Wednesday, November 02, 2005 2:09 PM

To: Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT visits by Dr.Sayre

Rose,

Just curious as to the nature of the SUPPORT Study visits that Dr. Maribeth Sayre is scheduling. Is this just a PR meet and greet and tour of the sites at our center? She did mention that she wanted to know if we had any problems or suggestions --- and I assume that only deals with the Masimo equipment, not other study issues. What information is she privy to? A few guidelines would be helpful.

Thank you.

Nancy P.

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; "Nancy Peters"
Cc: moshea@wfubmc.edu; "Das, Abhik"; "wade"
Subject: RE: SUPPORT visits by Dr.Sayre
Date: Thursday, November 03, 2005 12:44:54 AM

Hi Nancy
You have no obligations to Masimo.
We will try to get top the bottom of this
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 02, 2005 12:47 PM
To: Nancy Peters
Cc: moshea@wfubmc.edu; nfiner@ucsd.edu; Das, Abhik
Subject: RE: SUPPORT visits by Dr.Sayre

Nancy
There are no monitoring visits for this trial by the Massimo folks.

Thanks
Rose

From: Nancy Peters [mailto:npeters@wfubmc.edu]
Sent: Wednesday, November 02, 2005 3:35 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT visits by Dr.Sayre

Rose,

Correct, she is the Director of Medical Affairs for Masimo. I wanted to be sure that I understood the nature of her visit ("meet and greet" but no "show and tell"). Since we had received no official word that there would be a monitoring visit, I was a bit surprised when I received her telephone call and began wondering about what my obligations were to her. Thank you for the information.....it will help me in scheduling her visit.

Nancy

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 02, 2005 3:03 PM
To: Nancy Peters
Cc: nfiner@ucsd.edu; Michael O`Shea; Das, Abhik
Subject: RE: SUPPORT visits by Dr.Sayre

Hi Nancy,
It is my understanding that Dr. Sayre is with Massimo, correct? If so, she should discuss only the equipment. No patient information or study data can be shared with her.

Thanks for asking!
Rose

From: Nancy Peters [mailto:npeters@wfubmc.edu]

Sent: Wednesday, November 02, 2005 2:09 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT visits by Dr.Sayre

Rose,

Just curious as to the nature of the SUPPORT Study visits that Dr. Maribeth Sayre is scheduling. Is this just a PR meet and greet and tour of the sites at our center? She did mention that she wanted to know if we had any problems or suggestions --- and I assume that only deals with the Masimo equipment, not other study issues. What information is she privy to? A few guidelines would be helpful.

Thank you.

Nancy P.

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Cc: Poole, W. Kenneth
Subject: RE: SUPPORT visits by Dr.Sayre
Date: Wednesday, November 02, 2005 2:56:44 PM

I wouldn't show her any data. I think this should be restricted to specific issues about the equipment.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 02, 2005 2:20 PM
To: Das, Abhik; nfiner@ucsd.edu
Subject: FW: SUPPORT visits by Dr.Sayre

Abhik or Neil
Can you help me out here??
Thanks
Rose

From: Nancy Peters [mailto:npeters@wfubmc.edu]
Sent: Wednesday, November 02, 2005 2:09 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT visits by Dr.Sayre

Rose,

Just curious as to the nature of the SUPPORT Study visits that Dr. Maribeth Sayre is scheduling. Is this just a PR meet and greet and tour of the sites at our center? She did mention that she wanted to know if we had any problems or suggestions --- and I assume that only deals with the Masimo equipment, not other study issues. What information is she privy to? A few guidelines would be helpful.

Thank you.

Nancy P.

From: Shankaran, Seetha
To: Pappas, Athina
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Follow-up Conf Call - Tues Nov 1 at 2pm EST
Date: Tuesday, November 01, 2005 6:31:26 AM

Athina
I will bring this up
Thanks for your input
Seetha

SUPPORT TRIAL COMMENTS

NICU Discharge-Baseline Interview

p.1 Many parents may not understand what is meant by wheezing. Will the audiotape used for subsequent interviews be utilized?

Also, in section describing contents of diary may want to indicate that subsequent contact may be by phone or face-to-face interview.

p.3 14a. Don't know should be option 3

p.4 Under Father. Should change "Does she have bronchitis..." to Does *he* have bronchitis

Is there a page 5?

p. 6 Table Paternal Grandfather repeated. Need to change to paternal grandmother.

p.7 The parent or caregiver who completed the initial interview is requested to complete this interview. What if not primary caregiver?

Some of our families may not remember agreeing to the follow-up component. May need to remind them what the study entails. Would also be

a good idea to review follow-up at time of discharge for all surviving patients.

p. 9 It may be helpful to explain what is meant by wheezing/play audiotape prior to Q6.

Question 9. What if they answer 2 or 3 to 9 and then 1 to 9a. Or subsequently change their response to 9 after hearing audiotape. What response should be recorded? Initial or subsequent?

p. 11 Question 12. "...change for..." should be change *your *Question 13 Will miss those patients with wheezing/ bronchospasm whose physicians diagnose with exacerbation of BPD
*

*p.14 Prednisolone not included as a systemic steroid

p.15 target window for interview should be 18-22 months not 8-22

p.17 Again, may want to define what is meant by wheezing prior to question 6

p.20 Question 16a. Does this question refer to past 6 months only or in total. May need to clarify for parent.

p.21 Intro to Question 27 states "last 2 questions" However, there are more that 2 questions.

p.22 Question 29. Difficult to say how many colds per year usually as <2y.

From: Tyson, Jon E
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT GROWTH SECONDARY
Date: Tuesday, November 01, 2005 4:22:02 PM

Thanks.

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

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 01, 2005 12:54 PM
To: Tyson, Jon E
Subject: RE: SUPPORT GROWTH SECONDARY

Jon
The SUPPORT growth secondary group had a call today. The steering committee has approved the protocol to go forward without dollars at this point in time. There will be a vote in April 2006 for the financial part of the study. The data collection has been markedly decreased. We have a one page form which will be distributed within the next week or two.

Thanks
Rose
From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]
Sent: Wednesday, September 21, 2005 2:21 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT GROWTH SECONDARY

Rose, following the presentation, there was concern raised about the costs and the extent of data collection that was to be raised. If the investigators are willing, perhaps they would like to consider any further changes before the vote.

I wasn't on the conference call when it was discussed and neglected to give Shahnaz any suggestion but would be happy to do so if she wants to modify it

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

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 20, 2005 3:25 PM

To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E; Walid Salhab (Walid Salhab)
Cc: Petrie, Carolyn
Subject: SUPPORT GROWTH SECONDARY

HI,
I need a vote from the PI's regarding the SUPPORT GROWTH SECONDARY presented by Dr. Duara last week at the steering committee meeting.

Please indicate your preference:

1. Yes – this needs to go forward without additional funding and should start now
2. Yes – this needs to go forward and we should commit funds from the 2006 budget (this will impact the possibility of other protocols being instituted)
3. No – this needs to wait for the next budget period with reassessment in April 2006
4. No – this should not be done

I have attached the protocol.
Send me your vote by September 30.

Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Brenda Poindexter
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT Growth Secondary Study
Date: Tuesday, November 01, 2005 1:22:35 PM

Thanks Rose – if you have a minute after this call is over, let me know – I have some additional information about the nebulizer for the IPGE study. The RT's and I have spent the morning working with the nebulizer – we put methylene blue in a NS solution so we could actually see what happens – very interesting.....
Brenda

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Wednesday, October 19, 2005 11:24 AM
To: sduara@miami.edu; richard.ehrenkranz@yale.edu; bpoindex@iupui.edu; Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD); Hastings, Betty J.; Petrie, Carolyn
Subject: SUPPORT Growth Secondary Study

Dear All

Please send me your availability for a conference call to discuuss the SUPPORT secondary study. Attached for your review is the Nutritional Intake Form (GRO-01)

Monday Oct. 24
Tuesday Oct. 25
Wednesday Oct. 26
Thursday Oct. 27
Friday Oct. 28

Monday Oct. 31
Tuesday Nov. 1
Wednesday Nov. 2
Thursday Nov. 3
Friday Nov. 4

Monday Nov. 7
Tuesday Nov. 8
Wednassday Nov. 9
Thursday Nov. 10
Friday Nov. 11

Thanks,
Kris

Kristin Zaterka-Baxter
RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT Follow-up Conf Call - Tues Nov 1 at 2pm EST
Date: Tuesday, November 01, 2005 10:11:36 AM

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, November 01, 2005 9:54 AM
To: Petrie, Carolyn
Subject: RE: SUPPORT Follow-up Conf Call - Tues Nov 1 at 2pm EST

yes, I am planning to call in to 'stand by' as support for Dr. Stevens.
Dale

Dale L. Phelps, MD
Professor of Pediatrics and Ophthalmology
Division of Neonatology
University of Rochester

585.275.2972
dale_phelps@urmc.rochester.edu

> -----Original Message-----
> **From:** Petrie, Carolyn [mailto:petrie@rti.org]
> **Sent:** Tuesday, November 01, 2005 9:23 AM
> **To:** Phelps, Dale
> **Subject:** FW: SUPPORT Follow-up Conf Call - Tues Nov 1 at 2pm EST
>
> Dale—
>
> Are you able to join this call today?
>
> Carolyn

> **From:** Newman, Jamie
> **Sent:** Tuesday, October 25, 2005 1:49 PM
> **To:** Timothy_Stevens@URMC.Rochester.edu; richard.ehrenkranz@yale.edu; jon.e.tyson@uth.tmc.edu; MPeralta@PEDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; apappas@med.wayne.edu; sshankar@med.wayne.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; rdillard@wfubmc.edu; gary_myers@urmc.rochester.edu; bvohr@wihri.org; adusick@iupui.edu; steichjj@email.uc.edu; (b) (6)
> **Cc:** higginsr@mail.nih.gov; Betty Vohr; Das, Abhik; maegan.c.currence@uth.tmc.edu; SEguaras@med.miami.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; Janet.Morgan@childrens.com; VPhillips@peds.uab.edu; mgfuller@ucsd.edu; lnoel@wihri.org; ldrichar@iupui.edu; lohme001@mc.duke.edu; bjacksn@wfubmc.edu; diane_hust@urmc.rochester.edu; mbball@leland.stanford.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; ellen_hale@oz.ped.emory.edu; dkennedy@dmc.org; Jackie.Hickman@Childrens.com; bss5@cwru.edu; joanne.williams@yale.edu; Hastings, Betty J.; Petrie, Carolyn
> **Subject:** SUPPORT Follow-up Conf Call - Tues Nov 1 at 2pm EST

Dear Follow-up PI's,

Please note that a conference call to review the SUPPORT Follow-up study documents (Manual of Operations, forms, respiratory diary) will be held **Tuesday, November 1 from 2 - 3pm EST.** If you are not able to join this call please submit your comments via email or ask your follow-up coordinator to serve as your proxy. We look forward to hearing your comments on the study documents.

The call-in information is as follows:

USA Toll Free Number: 888-994(b) (6)
PASSCODE(b) (6)
LEADER: DR ROSEMARY HIGGINS

Thank you,

Jamie E. Newman, MPH
Statistics Research Division
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Betty Vohr
To: Roy Heyne; drficmd@aol.com; steichjj@email.uc.edu; adusick@iupui.edu; golds005@mc.duke.edu; apappas@med.wayne.edu; sshankar@med.wayne.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; MPeralta@peds.uab.edu; newman@rti.org; srhintz@stanford.edu; yvaucher@ucsd.edu; gary_myers@urmc.rochester.edu; Timothy_Stevens@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; rdillard@wfubmc.edu; richard.ehrenkranz@yale.edu
Cc: JACKIE Hickman; JANET MORGAN; bss5@cwru.edu; dkennedy@dmc.org; ldrichar@iupui.edu; mbball@leland.stanford.edu; Higgins, Rosemary (NIH/NICHD) [E]; lohme001@mc.duke.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; SEguaras@med.miami.edu; ellen_hale@oz.ped.emory.edu; VPhillips@peds.uab.edu; adas@rti.org; bkh@rti.org; petrie@rti.org; Teresa.Gratton@uc.edu; mgfuller@ucsd.edu; diane_hust@urmc.rochester.edu; maegan.c.currence@uth.tmc.edu; bjacksn@wfubmc.edu; Lucy Noel; elaine.romano@yale.edu; joanne.williams@yale.edu
Subject: RE: Reminder: SUPPORT Follow-up Conf Call - Tues Nov 1 at 2pmEST
Date: Monday, October 31, 2005 6:57:24 PM

You are absolutely correct. This situation arose over the fact that home visits are encouraged for non-compliant families, and may be made by a psychometrist or psychologist with a coordinator, nurse etc. and the physician is not always a part of the home-visit assessment team. Another example is when the physician goes on a home visit with a severely handicapped child (example spastic quad, blind, deaf etc) and attributes a 49 to the Bayley. Most sites do not permit a single person to do home visits.That individual or a second clinic professional can be trained to appropriately ask the questions on the NFO5. It is an issue currently at Indiana since the IRB states that it must specifically stipulate in the manual who the person (s) are who are qualified to do the specific component of the assessment. Only the trained professional who saw the child would obviously fill out the form. There is a lot of cross training at sites for efficiency purposes, which is a good idea and contributes to improved compliance with the protocol. We can discuss this further tomorrow with the group. It may be at some sites such as yours that a physician goes on all home visits and it is a non-issue.

From: Roy Heyne [mailto:Roy.Heyne@UTSouthwestern.edu]
Sent: Mon 10/31/2005 5:13 PM
To: [redacted]; steichjj@email.uc.edu; adusick@iupui.edu; golds005@mc.duke.edu; apappas@med.wayne.edu; sshankar@med.wayne.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; MTPeralta@peds.uab.edu; newman@rti.org; srhintz@stanford.edu; yvaucher@ucsd.edu; gary_myers@urmc.rochester.edu; Timothy_Stevens@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; rdillard@wfubmc.edu; Betty Vohr; richard.ehrenkranz@yale.edu
Cc: JACKIE Hickman; JANET MORGAN; bss5@cwru.edu; dkennedy@dmc.org; ldrichar@iupui.edu; mbball@leland.stanford.edu; higginsr@mail.nih.gov; lohme001@mc.duke.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; SEguaras@med.miami.edu; ellen_hale@oz.ped.emory.edu; VPhillips@peds.uab.edu; adas@rti.org; bkh@rti.org; petrie@rti.org; Teresa.Gratton@uc.edu; mgfuller@ucsd.edu; diane_hust@urmc.rochester.edu; maegan.c.currence@uth.tmc.edu; bjacksn@wfubmc.edu; Lucy Noel; elaine.romano@yale.edu; joanne.williams@yale.edu
Subject: RE: Reminder: SUPPORT Follow-up Conf Call - Tues Nov 1 at 2pmEST

I'm not clear on exactly what change is being proposed re who can fill out the NF05. Sounds like some consideration is being given to extending this beyond the group of interrator-certified/trained medical practitioners. First of all, given how much discussion/debate we have had among ourselves about where/how to draw the line on some of these critical assessment items, I think we should be very cautious about delegating these skills to others with less appreciation/experience in neuromotor exam/assessment. Secondly, I don't think we can have one person assess some of the items and another draw the conclusions.

>>> "Betty Vohr" <BVohr@WIHRI.org> 10/31/05 3:24 PM >>>
Greetings all. I am ccing you on emails that were initiated by Anna Dusick. It involves a minor change in the manual stipulating who can fill ou the NFO5. I hope that we can approve this at the end of the conference call for Support. The basic request is to describe and expand who can fill this out. Some IRBs are very directive in this regard.

From: Betty Vohr [mailto:BVohr@WIHRI.org]
Sent: Monday, October 31, 2005 2:59 PM
To: Dusick, Anna M.
Subject: RE: NFO5 and the manual

I think we need to remember that their are tremendous site differences in how this is carried out.

From: Dusick, Anna M. [mailto:adusick@iupui.edu]
Sent: Monday, October 31, 2005 2:57 PM
To: Betty Vohr
Subject: RE: NFO5 and the manual

This is interesting as the judgement parts (GMFS, hand and UE coordination) may require some training that a psychologist/psychometrist has. In some cases, the study nurse coordinator will not have the skills for the GMFS or the hand and UE coordination items. I was hoping to get away from that discussion and to keep the data entry tight. Also, it does not quite fit with my rationale, as an LPN for example, may not have the skills for hand function assessment. I added it anyway. See what you think.

I would keep the term Study nurse, coordinator etc. so we do not get into human subjects violations and not use "other trained clinical staff person". We cannot, for example "deputize" another staff person for the day we are away.

What are your thoughts on asterisking the items on the NF05 that the non-Neuroexaminer can complete? In the case of an audit, the study police would look for wrongly entered items not permitted by the protocol, and we want to keep the integrity of the data. As PI it would be each of our responsibility to be sure just the permitted parts of the NF05 are completed by a non-neuro examiner. This may be more than some want to do. For example, even if obvious, the Study personnel cannot answer the CP diagnosis unless a neuro-examiner.

From: Newman, Jamie [mailto:newman@rti.org]
Sent: Monday, October 31, 2005 8:02 AM

To: Timothy_Stevens@URMC.Rochester.edu; richard.ehrenkranz@yale.edu; jon.e.tyson@uth.tmc.edu; MPeralta@PEDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; apappas@med.wayne.edu; sshankar@med.wayne.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; rdillard@wfubmc.edu; gary_myers@urmc.rochester.edu; Betty Vohr; adusick@iupui.edu; steichjj@email.uc.edu; (b) (6)
Cc: higginsr@mail.nih.gov; Betty Vohr; Das, Abhik; maegan.c.currence@uth.tmc.edu; SEguaras@med.miami.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; Janet.Morgan@childrens.com; VPhillips@peds.uab.edu; mgfuller@ucsd.edu; Lucy Noel; ldrichar@iupui.edu; lohme001@mc.duke.edu; bjacksn@wfubmc.edu; diane_hust@urmc.rochester.edu; mbball@leland.stanford.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; ellen_hale@oz.ped.emory.edu; dkennedy@dmc.org; Jackie.Hickman@Childrens.com; bss5@cwru.edu; joanne.williams@yale.edu; Hastings, Betty J.; Petrie, Carolyn
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Where impairment is defined as any restriction or lack of ability to perform within the range considered as normal or if there is chronic otitis media with associated delayed speech skills.

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Code '0' if no hearing aid has been prescribed by a hearing specialist.

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The call-in information is as follows:

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PASSCODE: (b) (6)

LEADER: DR ROSEMARY HIGGINS

Thank you,

Jamie E. Newman, MPH

Statistics Research Division

RTI International

Telephone: (919) 485-5719

Fax: (919) 485-7762

newman@rti.org

From: Neil Finer
To: "Michael O`Shea"; "Susan Hintz"
Cc: Higgins, Rosemary (NIH/NICHD) [E]; wrich@ucsd.edu
Subject: RE: MRI Secondary for SUPORT
Date: Monday, October 31, 2005 11:12:39 AM

Hi Mike and Susan
The use of the baby bean bag seems to work very well. Our center has a very active MR program and getting to the magnet and taking up time is a prime issue. I would recommend that you consider this type of device. We will be doing 3 more infant today and tomorrow, and if this works, I would probably suggest that we send out some information about it with pictures. I'll keep you informed.
I agree with Susan, but would suggest that your IRB let the parents judge the benefit vs risk in view of the information that can be oobtained.
Neil

From: Michael O`Shea [mailto:moshea@wfubmc.edu]
Sent: Monday, October 31, 2005 6:43 AM
To: Susan Hintz
Cc: neil finer; higginsr@mail.nih.gov
Subject: RE: MRI Secondary for SUPORT

Susan,
Thanks so much for your fast response. Assuming Neil agrees, we will proceed as you have suggested.
Mike

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Friday, October 28, 2005 6:39 PM
To: Michael O`Shea
Cc: neil finer; higginsr@mail.nih.gov
Subject: Re: MRI Secondary for SUPORT

Mike,

Thank you for your note.

1) First, I want to make sure that the concept of "congenital infection" is clear in the secondary - I am specifically talking about TORCH infections/HIV/syphylis, not something like GBS or E.Coli. I was really only trying to eliminate a potentially powerfully confounding variable. My suggestion would be to state that any head imaging would only be used in the STUDY if TORCH infections are not suspected. I think that is pretty much what you suggested below.

2) There is no doubt that white matter injury can be better visualized on MRI than US. The follow-on point is that neuromotor outcome is linked to white matter development/injury and that this is a major issue in neurodevelopmental outcome in the preterm infant. Your recent review (with Serena Counsell and Professor Dammann) is wonderful and quite comprehensive, and I think you spell out well the limitations and positive points of the few studies that have been published of head-to-head comparisons of MRI and US in predicting outcome. If a counterargument from your colleagues includes the work of Linda de Vries - which is incredibly great work - you might point out that Dr. deVries did WEEKLY ultrasounds to get the good results she got. You might also point to the work of Wilson-Costello and recently of Abbott Laptook underscoring the limitations of ultrasound alone with respect to explaining adverse neurodevelopmental outcomes among premies.

Bottom line, if YOU can't convince your colleagues and IRB with your considerable debating powers and knowledge, I am not sure it can be done. If they can't be convinced, I agree that the best option is to indicate that two attempts will be made without sedation, then forget it.

By the way, Wade Rich (UCSD's wonderful coordinator) and I have become best friends by email - he has managed to get MRI's of two SUPPORT patients without sedation - and their site had not previously used that technique, so it was new. Maybe the sedation won't be needed?? Hopefully...

Susan

> Susan and Neil,
>
> Our IRB has raised a couple of questions about the MRI Secondary and I'm hoping you can help with the answers.
>
> 1) The main SUPPORT Trial does not have as one of its exclusion criteria congenital infection, whereas the secondary MRI study lists congenital infection as an exclusion criteria. If a center desires, as we do, to have a single consent form (similar to the Stanford consent form which Susan distributed as a template) the discrepancy between the exclusion criteria for the primary and secondary studies raises a problem. Specifically, if a child is enrolled in SUPPORT and then after delivery the diagnosis is made of a congenital infection, it would seem that the child becomes ineligible for the secondary. If this correct, then then consent form needs to state that the MRI will be done only on those infants who are not found to have a congenital infection, right?
>
> 2) In the past our IRB has not approved the use of conscious sedation for research studies unless there is a prospect of benefit to the child. While I understand that some neonatologists and radiologists feel that there is clinical benefit to an MRI, this is a difficult position to adopt here where we obtain both an early and a late cranial ultrasound and so the issue becomes not whether the MRI is beneficial but whether it is beneficial in a child who already has information from two ultrasounds. I am not convinced that this is the case nor are my colleagues. That presents several options:
>
> -- Perhaps you can provide a convincing argument that I can use to convince my colleagues and the IRB that the MRI holds the potential for benefit
>
> --- alternatively we can try the feed and wrap approach, and if it fails, try again the next day, and if it fails again, throw in the towel and accept the fact that this study participant will not have MRI data
>
> Thanks for your guidance on these issues.
>
> Mike

From: Das, Abhik
To: Daniel K Benjamin; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Hastings, Betty J.; Zaterka-Baxter, Kristin
Subject: RE: infant enrolled at less than 401 grams
Date: Monday, October 31, 2005 8:39:15 AM

Let us keep this baby in the study. For future reference, we can send out a memo to the sites that only GDB babies should be considered for inclusion in the Candidiasis study.

Thanks

Abhik

-----Original Message-----
From: Daniel K Benjamin [mailto:benja005@mc.duke.edu]
Sent: Monday, October 31, 2005 8:18 AM
To: Phelps, Dale
Cc: Das, Abhik; 'Higgins, Rosemary (NIH/NICHD)'; Poole, W. Kenneth
Subject: RE: infant enrolled at less than 401 grams

It was our intent to have GDB babies in the study because the GDB database and candida database could be reconcilled for some of the information for the candida study. For example some potential morbidities (such as ROP) rely on the GDB. My concern is that when we developed the CRFs for the candida study, the candida steering committee consistently thought (and said) 'we will have GDB' when deciding on capture elements.

However, the crucial elements (blood results and CAO3-CA06) will not be missing for this infant. So my thinking is

1) This baby should stay in the study for reasons Dale has outlined
2) We should remind coordinators that infants should be enrolled in GDB to get into Candida study.

danny

Danny Benjamin MD PhD MPH
Associate Professor Duke University

PO Box 17969
Duke Clinical Research Institute
Durham NC 27705
Ph: 919-668-8295
Fax: 919-668-7058

"Phelps, Dale"
<Dale_Phelps@URMC.Rochester.edu>

10/31/2005 08:08 AM

To "'Higgins, Rosemary (NIH/NICHD)'" <higginsr@mail.nih.gov>, "Das, Abhik" <adas@rti.org>, Daniel K Benjamin <benja005@mc.duke.edu>, "Poole, W. Kenneth" <poo@rti.org>

cc

Subject RE: infant enrolled at less than 401 grams

Hi all,

I think because the protocol specifies infants of <1000g

And
The infant's mother has been approached and already has consented to be in the study, that we should include this infant.
(There is no additional cost because the GDB data are already being completed because the infant was enrolled in the SUPPORT study.)

I could propose for the future that an infant of <1000g BW who is also less than 401 grams could also be enrolled in the Candidiasis study IF she/he had been enrolled in SUPPORT. (this will make them 24 weeks or older)

If, however, the RTI database is going to have problems because the BW is outside the parameters permitted for analyses, I could understand why the future plan would be not to include infants of less than 401g.

Also, if the majority vote is that this infant not be in Candidiasis, I would understand. Just let us know so that we don't collect samples on the baby.

Dale

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 31, 2005 7:58 AM
To: Phelps, Dale; Das, Abhik; Daniel K Benjamin; Poole, W. Kenneth
Subject: RE: infant enrolled at less than 401 grams

HOw should we approach this individual baby - leave in or take out??
Rose

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Fri 10/28/2005 4:55 PM
To: 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD); Daniel K Benjamin; Poole, W. Kenneth
Subject: RE: infant enrolled at less than 401 grams

The mother has consented already.
Dale Phelps

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, October 28, 2005 12:03 PM
To: Higgins, Rosemary (NIH/NICHD); Daniel K Benjamin; Poole, W. Kenneth
Cc: Phelps, Dale
Subject: RE: infant enrolled at less than 401 grams

For the sake of consistency I dont think any data from this baby should be used in analyses for this study. So, I would recommend stopping the data collection unless it is not prudent for the site to do that at this stage (since they have already approached and consented the mother about this study).

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 28, 2005 11:53 AM
To: Daniel K Benjamin; Das, Abhik; Poole, W. Kenneth
Cc: Phelps, Dale
Subject: RE: infant enrolled at less than 401 grams

Danny

I had spoken to Abhik and Ken about this. The baby was included in SUPPORT and therefore GDB forms were filled out due to SUPPORT. This was addressed up front in SUPPORT, but never discussed in candida with respect to infants < 401 grams. Since we were almost close to halfway on candida, we thought that these infants should not be included in the trial (as they have not been recruited thus far). This is a fluke as the child was enrolled in SUPPORT. As far as continuing to obtain samples, I would defer to the data center.

Rose

From: Daniel K Benjamin [mailto:benja005@mc.duke.edu]
Sent: Friday, October 28, 2005 11:49 AM

To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: infant enrolled at less than 401 grams

Rose, can we give a protocol exemption for this baby? Do NRN trials do that similar to industry?

Sorry about mix up regarding coordinator call.

danny

Danny Benjamin MD PhD MPH
Associate Professor Duke University

PO Box 17969
Duke Clinical Research Institute
Durham NC 27705
Ph: 919-668-8295
Fax: 919-668-7058

"Reubens, Linda" <Linda_Reubens@URMC.Rochester.edu>

10/24/2005 10:17 AM

To

"'danny.benjamin@duke.edu'" <danny.benjamin@duke.edu>

cc

Subject

infant enrolled at less than 401 grams

Hi Danny,
We have a baby that we put in the GDB at less than 401 grams because the baby was enrolled in SUPPORT. Because she was in the GDB, we enrolled her in Candidiasis. Last Thursday, Rose told us on the coordinator's call that infants less than 401 are not eligible for Candidiasis. What should we do with this baby? Should we continue to obtain samples, or stop?
Linda

From: Newman, Jamie
To: Timothy_Stevens@URMC.Rochester.edu; richard.ehrenkranz@yale.edu; jon.e.tyson@uth.tmc.edu; MPeralta@PEDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; apappas@med.wayne.edu; sshankar@med.wayne.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; rdillard@wfubmc.edu; gary_myers@urmc.rochester.edu; byohr@wihri.org; adusick@iupui.edu; steichji@email.uc.edu; (b) (6)
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Betty Vohr; Das, Abhik; maegan.c.currence@uth.tmc.edu; SEguaras@med.miami.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; Janet.Morgan@childrens.com; VPhillips@peds.uab.edu; mgfuller@ucsd.edu; inoel@wihri.org; ldrichar@iupui.edu; lohme001@mc.duke.edu; bjacksn@wfubmc.edu; diane_hust@urmc.rochester.edu; mbball@leland.stanford.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; ellen_hale@oz.ped.emory.edu; dkennedy@dmc.org; Jackie.Hickman@Childrens.com; bss5@cwru.edu; joanne.williams@yale.edu; Hastings, Betty J.; Petrie, Carolyn
Subject: Reminder: SUPPORT Follow-up Conf Call - Tues Nov 1 at 2pm EST
Date: Monday, October 31, 2005 8:02:17 AM
Attachments: aEEGF09 BayleyScales jn.DOC

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LEADER: DR ROSEMARY HIGGINS

Thank you,

Jamie E. Newman, MPH
Statistics Research Division
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

aEEG FOLLOW-UP STUDY

BAYLEY SCALES SUMMARY SCORE SHEET

Center No. __ __ Site : __ Study No: H __ __ __ __ Follow-Up No. AFN __ __ Mother's Initials: __ __ __ Birth No: ____

This form should be completed for all children seen at the 18 + 4 month visit.

A. BAYLEY INFORMATION

1. Adjusted age: __ __ Months

2. Was the child Bayley testable? Y N N

a. If NO, not tested due to severe motor or developmental delay (see reason codes below and enter all that apply): __ __ __ __ __

Codes for reason not tested:	
1 = Blindness	3 = Motor impairment
2 = Deafness	4 = Cognitive impairment

b. Bayley Scales of Infant Development:

1. MDI: (enter "049" if answer was NO to Question 2) __ __ __

2. PDI: (enter "049" if answer was NO to Question 2) __ __ __

3. Behavior rating scale (percentiles)

a) Orientation/engagement: __ __ __

b) Emotional regulation: __ __ __

c) Motor quality: __ __ __

d) Total raw score: __ __ __

c. Was Bayley Exam conducted in English? Y N

1) If No, was an interpreter required? Y N

d. Was the Bayley Examiner masked to the child's medical history? Y N

B. FORM COMPLETION

1. Where was the Bayley conducted? __

1 = Clinic	3 = Other Clinic	9= Other
2 = Home	4 = Hospital	

2. Date of Bayley Exam: __ __ / __ __ / __ __ __ __ (Month Day Year)

3. Initials of person administering Bayley Exam: __ __ __

From: Newman, Jamie
To: Shankaran, Seetha
Cc: Becky; Higgins, Rosemary (NIH/NICHD) [E]
Subject: aEEG Follow-up items for SUPPORT Conf Call
Date: Thursday, October 27, 2005 4:40:18 PM
Attachments: aEEGF09[BayleyScales]in.DOC

Seetha,
We have had extreme difficulties in finding a day that maximizes participation for this call. Nov 1 seemed to work for the highest number of people. Attached is the revised aEEGF09 (Bayley Scales Summary Score Sheet) based on my discussion with Becky. Please let me know if I have accurately captured the revisions and I will send it out before the call on Tuesday.

You mention sending the group the Infant Examination Form (aEEGF05) as well but we did not make changes to the form, we just made some clarifications in the MOO. Below is the relevant section of the form and the corresponding description in the MOO. Will it be sufficient to simply send the text below rather than the entire form since changes will not be made to the form?

b. Hearing impaired: ___

1 = No apparent functional impairment 2 = Impairment

1) If impairment (2), hearing aid requirement: ___

0 = None 1 = Right only 2 = Left only 3 = Both

b. Hearing impaired:

Code '1' if no apparent functional impairment at the time of this assessment.
Code '2' if impairment at the time of this assessment.

Where impairment is defined as any restriction or lack of ability to perform within the range considered as normal or if there is chronic otitis media with associated delayed speech skills.

1) If Impairment (2), hearing aid requirement:

Code '0' if no hearing aid has been prescribed by a hearing specialist.
Code '1' if hearing aid has been prescribed by a hearing specialist for the right ear only.
Code '2' if hearing aid has been prescribed by a hearing specialist for the left ear only.
Code '3' if hearing aid has been prescribed by a hearing specialist for both ears.

Thanks, Jamie

Jamie E. Newman, MPH
Statistics Research Division
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Thursday, October 27, 2005 12:46 PM
To: Newman, Jamie
Cc: Becky; higginsr@mail.nih.gov
Subject: RE: SUPPORT Follow-up Conf Call - Tues Nov 1 at 2pm EST

Jamie
Nov 1 is a very bad day for me but that is the only day available , right? I need to speak to all the FU PI's so this is the only opportunity so I will have to attend

I would like to start at beginning of the call (2 PM) and briefly do the following

a) Update on aEEG FU forms and manual

b) Changes from the Hypothermia trial forms: 1) hearing assessment clarification and 2) Bayley summary forms---I would like you to send the 2 forms that we are discussing (the hearing assessment and the Bayley summary form) to all so they can see what I am talking about. Becky has gone over this with you

c) Changes to Extended FU study as discussed on last conference call

d) need to get data on SES/maternal education/ on all subjects

Anything else, Becky or Rose?

Thanks
SS

----Original Message-----
From: Newman, Jamie [mailto:newman@rti.org]
Sent: Thursday, October 27, 2005 10:01 AM
To: Shankaran, Seetha; higginsr@mail.nih.gov
Cc: Townsend, Katrice
Subject: RE: SUPPORT Follow-up Conf Call - Tues Nov 1 at 2pm EST

> That is fine with me, however, Rose is out of the office this week so she may not respond until she gets back. You mentioned earlier that Nov 1 was a bad day for you and that you would not be able to join. Will you be joining the call? Please provide me with some specifics on what you would like to cover concerning aEEG follow-up (a few bulleted points) so that I can include it in the agenda when I send out the call reminder.
>
> Thanks, Jamie
>
> Jamie E. Newman, MPH
> Statistics Research Division
> RTI International
> Telephone: (919) 485-5719
> Fax: (919) 485-7762
> newman@rti.org

> **From:** Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
> **Sent:** Wednesday, October 26, 2005 11:10 AM
> **To:** Newman, Jamie; higginsr@mail.nih.gov
> **Cc:** Townsend, Katrice
> **Subject:** RE: SUPPORT Follow-up Conf Call - Tues Nov 1 at 2pm EST

Rose and Jamie
I did request 15 minutes at end of call, I do need to talk about aEEG follow up, so can you add to agenda too--It might be ages before all FU PI's are on a call again
Thanks
Seetha

-----Original Message-----
From: Newman, Jamie [mailto:newman@rti.org]
Sent: Tuesday, October 25, 2005 1:49 PM
To: Timothy_Stevens@URMC.Rochester.edu; richard.ehrenkranz@yale.edu; jon.e.tyson@uth.tmc.edu; MPeralta@PEDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; Pappas, Athina; Shankaran, Seetha; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; rdillard@wfubmc.edu; gary_myers@URMC.Rochester.edu; bvohr@wihri.org; adusick@iupui.edu; steichjj@email.uc.edu; (b) (6)
Cc: higginsr@mail.nih.gov; Betty Vohr; Das, Abhik; maegan.c.currence@uth.tmc.edu; SEguaras@med.miami.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; Janet.Morgan@childrens.com; VPhillips@PEDS.UAB.EDU; mgfuller@ucsd.edu; lnoel@wihri.org; ldrichar@iupui.edu; lohme001@mc.duke.edu; bjacksn@wfubmc.edu; diane_hust@URMC.Rochester.edu; mbball@leland.stanford.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; ellen_hale@oz.ped.emory.edu; Kennedy, Deborah (DMC); Jackie.Hickman@childrens.com; bss5@cwru.edu; joanne.williams@yale.edu; Hastings, Betty J.; Petrie, Carolyn
Subject: SUPPORT Follow-up Conf Call - Tues Nov 1 at 2pm EST

Dear Follow-up PI's,

Please note that a conference call to review the SUPPORT Follow-up study documents (Manual of Operations, forms, respiratory diary) will be held **Tuesday, November 1 from 2 - 3pm EST.** If you are not able to join this call please submit your comments via email or ask your follow-up coordinator to serve as your proxy. We look forward to hearing your comments on the study documents.

The call-in information is as follows:

USA Toll Free Number: 888-994-8442
PASSCODE: 26499
LEADER: DR ROSEMARY HIGGINS

Thank you,

Jamie E. Newman, MPH
Statistics Research Division
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

aEEG FOLLOW-UP STUDY

BAYLEY SCALES SUMMARY SCORE SHEET

Center No. __ __ Site : __ Study No: H __ __ __ __ Follow-Up No. AFN __ __ Mother's Initials: __ __ __ Birth No: ____

This form should be completed for all children seen at the 18 + 4 month visit.

A. BAYLEY INFORMATION

1. Adjusted age: __ __ Months

2. Was the child Bayley testable? Y N N

a. If NO, not tested due to severe motor or developmental delay (see reason codes below and enter all that apply): __ __ __ __ —

Codes for reason not tested:	
1 = Blindness	3 = Motor impairment
2 = Deafness	4 = Cognitive impairment

b. Bayley Scales of Infant Development:

1. MDI: (enter 049 of NO to Question 2) — — —

2. PDI: (enter 049 of NO to Question 2) — — —

3. Behavior rating scale (percentiles)

a) Orientation/engagement: — — —

b) Emotional regulation: — — —

c) Motor quality: — — —

d) Total raw score: — — —

c. Was Bayley Exam conducted in English? Y N

1) If No, was an interpreter required? Y N

d. Was the Bayley Examiner masked to the child's medical history? Y N

B. FORM COMPLETION

1. Where was the Bayley conducted? —

1 = Clinic	3 = Other Clinic	9= Other	
2 = Home	4 = Hospital		

2. Date of Bayley Exam: __ __ / __ __ / __ __ __ __
Month Day Year

3. Initials of person administering Bayley Exam: — — —

From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT GROWTH SECONDARY
Date: Wednesday, October 26, 2005 9:19:13 AM

Sure - not certain I understand what Jon wants. Wasn't the protocol voted on as is and approved by PIs, realizing that there can only be new money after April 1? Definitely for discussion on the call
Shahnaz

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
To: sduara@miami.edu <sduara@miami.edu>
Sent: Tue Oct 25 13:56:06 2005
Subject: Fw: SUPPORT GROWTH SECONDARY

Shahnaz u
Can we discuss on the call when it gets set up??
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Tyson, Jon E <Jon.E.Tyson@uth.tmc.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Mon Oct 24 16:25:11 2005
Subject: RE: SUPPORT GROWTH SECONDARY

Sorry, in a hurry, did the investigators address the concerns about costs and extent of data collection? If so, did they send a cover letter to describe changes?

Jon E. Tyson, MD, MPH

Center for Clinical Research & Evidence-Based Medicine

UT Medical School at Houston

6431 Fannin St., MSB 2.106

Houston, TX 77030

voice 713-500-5651

fax 713-500-0519

From: Tyson, Jon E
Sent: Wednesday, September 21, 2005 1:21 PM
To: 'Higgins, Rosemary (NIH/NICHD)'
Subject: RE: SUPPORT GROWTH SECONDARY

Rose, following the presentation, there was concern raised about the costs and the extent of data collection that was to be raised. If the investigators are willing, perhaps they would like to consider any further changes before the vote.

I wasn't on the conference call when it was discussed and neglected to give Shahnaz any suggestion but would be happy to do so if she wants to modify it

Jon E. Tyson, MD, MPH

Center for Clinical Research & Evidence-Based Medicine

UT Medical School at Houston

6431 Fannin St., MSB 2.106

Houston, TX 77030

voice 713-500-5651

fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 20, 2005 3:25 PM
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E; Walid Salhab (Walid Salhab)
Cc: Petrie, Carolyn
Subject: SUPPORT GROWTH SECONDARY

HI,

I need a vote from the PI's regarding the SUPPORT GROWTH SECONDARY presented by Dr. Duara last week at the steering committee meeting.

Please indicate your preference:

1. Yes – this needs to go forward without additional funding and should start now
2. Yes – this needs to go forward and we should commit funds from the 2006 budget (this will impact the possibility of other protocols being instituted)
3. No – this needs to wait for the next budget period with reassessment in April 2006
4. No – this should not be done

I have attached the protocol.

Send me your vote by September 30.

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Neil Finer
To: "Kathleen Bridges"; wrich@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Pt question
Date: Monday, October 24, 2005 5:06:46 PM

Hi Kathleen

This sounds a tragic set of circumstances. I would recommend recording as extenuating circumstances as you have done.

Thanks for keeping us posted.

Be well

Neil

From: Kathleen Bridges [mailto:Kathleen.Bridges@cchmc.org]
Sent: Monday, October 24, 2005 11:49 AM
To: wrich@ucsd.edu
Cc: nfiner@ucsd.edu
Subject: SUPPORT Pt question

Hi Wade,
I have a few questions for you regarding a recent enrollee into the SUPPORT trial here at UC. here's the situation: Infant (b) (6) was born (b) (6) at 27 and 2/7 weeks gestation, and randomized into the control arm of the study. He required extensive active resuscitation (including chest compressions, 7 rounds of epi, multiple round of bicarb) over his first 40 minutes of life. (I have already submitted that resuscitation as an AE, btw). On the way back to the NICU, the team stopped with the baby in mom's recovery room for (b) (6). by the time they got the baby back, and retaped the ETT, then gave him surfactant (since it is policy here to give it back in the NICU), he was about 1.5 hours old. (so I have written that up as protocol deviation #1.)
On DOL #3 (b) (6), he met extubation criteria. However, he has not yet been extubated because he has no respiratory effort of his own. He has generalized hypotonia, little to no spontaneous movement, weak reponses to noxious stimuli, and absent gag reflex. He had a brief trial of CPAP via ETT, which he quickly failed. The suspected diagnosis is HIE at this point, though it has not been confirmed. (he has some mild dysmorphic features, and the possible diagnosis of congenital muscular dystrophy has been suggested by the neuro team.)
So, sorry to be so detailed, but I wanted to paint the complete picture for you. What is the best way to document this. Should I write up a second deviation? And if so, should I code it as #10 "other"? (I don't see it specifically listed in the previous 9 types of deviations.) Or should I capture it somewhere else as "extenuating circumstances" that have prevented his extubation? In the MOP on page 5-4 it states "Failure to attempt to extubate an infant meeting all of the above criteria will be recorded as a study protocol deviation unless extenuating circumstances are noted."
Your input would be greatly appreciated!
thanks, kate bridges

From: Zaterka-Baxter, Kristin
To: Navarrete, Cristina; sduara@miami.edu; richard.ehrenkranz@yale.edu; nfiner@ucsd.edu; Brenda Poindexter; Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Hastings, Betty J.; Petrie, Carolyn
Subject: SUPPORT Growth Secondary
Date: Monday, October 24, 2005 3:00:00 PM
Attachments: growthprot revised Aug 9 2005.doc
GRO-01 [Nutrition Data].doc

Dear All,

A conference call has been set up to discuss the SUPPORT Growth Secondary on **Tuesday, November 1st, 2005 from 1:00 – 2:00pm EST (10:00-11:00am PST).** Attached please find the protocol (revised 08/09/2005) and the nutritional data form for review.

To join the call:
Dial Toll free: **888-994-**(b) (6)
Pass code: (b) (6) **(# when prompted)**

Thank you for your time and if there are any questions regarding this schedule please don't hesitate to contact me by email or phone (919-485-7750).

Kris

Kristin Zaterka-Baxter
RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study: A Proposed Secondary Study

Cristina Navarrete MD, and Shahnaz Duara MD
University of Miami Miller School of Medicine, Miami, FL.

Abstract:

Post-natal growth restriction is a major problem in preterm infants. Perturbations in oxygenation are recognized to influence post-natal growth; hypoxic conditions can directly impair growth and hyperoxic conditions predispose infants to BPD, which in turn has been linked to poor growth. The NICHD Neonatal Network is conducting a prospective trial of preterm infants randomized to two levels of baseline oxygen saturations. The effect of baseline saturations on pulmonary morbidity and ROP are the primary outcome measures. With respect to post-natal growth, there is a paucity of data relating alterations in baseline oxygen saturation and/or frequent deviations above or below the baseline to growth outcomes. We propose a secondary study to quantify short-term growth velocity in-hospital and long-term growth at 18-22 months of corrected age for infants enrolled in the SUPPORT Trial in relationship to oxygen saturation.

A. Hypothesis to be tested

Primary:

1. Infants in the low oxygen saturation group (85-89%) will have better in-hospital and long-term (18-22 months corrected age) growth.

2. Trajectories of growth in hospital will be better for infants in the low oxygen saturation group.

Secondary:

1. Growth will be greater in infants who spend > 50% of the time with daily median oxygen saturation between 85% -95% while on supplemental oxygen, independent of randomization to low or high oxygen saturation.

2. Infants with BPD will have poorer in-hospital and long-term growth than infants without BPD, independent of the saturation randomization arm.

3. Better long-term growth will be positively related to neuro-developmental outcome, independent of the saturation randomization arm.

B. Specific Aims:

1. To determine anthropometric measurements (wt, HC, length) in infants randomized to low and high oxygen saturation arms, from birth to hospital discharge and again at 18-22 months corrected age.
2. To determine nutritional intake (parenteral and enteral) during hospital stay.
3. To determine the percentage of infants with growth <10 percentile at 36 weeks PMA or discharge, whichever comes first.
4. To determine the percentage of infants with growth <10 percentile at 18-22 months corrected age.
5. To determine growth in relation to the proportion of time spent with oxygen saturation
    a. <85% and >95%
    b. 85%-95%
6. To determine growth in relation to infants' median oxygen saturation while in supplemental oxygen
    a. median oxygen saturation > 95%
    b. median oxygen saturation 85% - 95%
    c. median oxygen saturation < 85%
7. To relate incidence of BPD in low and high saturation arms to growth.
8. To determine in-hospital growth velocity/trajectory in low and high saturation arms.
9. To determine long-term growth velocity/trajectory, from hospital discharge to follow up at 18-22 months corrected age in low and high saturation arms.
10. To relate neuro-developmental outcome at 18-22 months corrected age to long-term growth in low and high saturation arms.

Rationale:

The SUPPORT Trial will randomize infants to two ranges of SpO2 in order to test the hypothesis that use of a lower SpO2 range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity and/or the need for surgical intervention. Retrospective cohort data from several units in the U.K., with different oxygen supplementation policies, revealed poorer growth patterns in the preterm infants exposed to higher oxygen saturations for the duration of oxygen exposure (Tin 2001). Conversely, observational data of infants with established BPD show better growth with home oxygen support (Groothius 1987), and two recent RCT of different target saturations in older oxygen-dependent premature infants showed no difference in short or long-term growth outcomes (STOP-ROP 2000, BOOST Trial 2003). There are no RCT data evaluating the short or long-term growth impact of different SpO2 strategies with supplemental oxygen use in a birth cohort of extremely preterm infants. Therefore, this study provides an opportunity for us to

obtain critically needed growth information on premature infants who are exposed from birth to different target oxygen saturation strategies.

Background

Improvements in antenatal care, respiratory support and nutrition have contributed to increased survival of ELBW infants. As the number of survivors increase, the long term outcome of these infants becomes more important. Lemons et al described growth failure or weight <10th percentile at 36 weeks postmenstrual age in 97% of ELBW infants surviving to discharge. Some morbidities in adulthood are linked to growth during the early post-natal period (Singhal 2004) and make adequacy of growth in this population of heightened interest.

Instead of following intra-uterine growth curves of age matched fetuses, VLBW infants exhibit wide-spread post-natal growth retardation (Cooke 2004), losing ground during the first weeks of life (Berry 1997). To resume growth post-natally, nutrition is of paramount importance; however, other factors such as severity of illness and perhaps oxygenation also play a role. Observational studies of infants with BPD showed poor post-natal growth when infants were sent home without oxygen supplementation (Markestad 1981).

Although preterm infants without lung disease attain oxygen saturations >95%, artificial attempts to keep arterial oxygenation at a "physiological" level may not be beneficial to growth, the lung or retina (Tin 2001). Animal studies have shown that newborn mammals (mice, rats, guinea pigs) develop poor growth with chronic hypoxia and that blunted body growth is directly proportional to the profundity of the exposure to chronic hypoxia (Mortola 1990). Chronic hypoxemia has also been suggested as the cause of poor growth in patients with cyanotic congenital heart disease (Dundar 2000). When home oxygen supplementation was discontinued inappropriately by parents in a cohort of VLBW infants with BPD, there was a deceleration in the rate of weight gain, which improved when oxygen supplementation was resumed (Groothius 1987). Hudak et al in 1989 observed that ELBW infants with CLD who went home on oxygen supplementation had good catch-up growth at 19 months. Taken collectively, these data suggest that hypoxic conditions affect growth negatively and supplementing oxygen may improve growth.

The optimal level of oxygen saturation to promote post-natal growth is unknown. Most of the available human data is limited to oxygen supplementation of infants who are oxygen dependent or have BPD. Baraldi et al demonstrated that discharged infants with BPD, who were kept on supplemental oxygen to keep saturations above 94%, had progressive but poor weight gain (stayed below 3rd percentile) at 9 months corrected age follow-up. In infants with BPD whose oxygen supplementation was intentionally discontinued, the subset who exhibited episodes of desaturations below 88-91% had a significant decline in the rate of weight gain as compared to those who maintained saturations above 92% (Moyer-Mileur 1996). Conversely, when two different oxygen saturation control policies (high: 88-98% and low: 70-90%) were retrospectively reviewed in <28

week gestation infants, the infants being cared for in the high oxygen saturation policy units were more likely to weigh less than the 3rd percentile at discharge (45% vs. 17%, Tin 2001). The infants assigned to the high oxygen saturation limits were also more likely to have BPD and ROP.

Recently, the BOOST Trial demonstrated that randomizing infants born <30 weeks gestation who were still on oxygen at 32 weeks postmenstrual age either to standard saturations (91-94%) or to high saturations (95-98%) produced no significant difference in growth at 12 months corrected age. This study, while randomizing infants to two different levels of saturations (conventional and high), only enrolled infants if they were still on oxygen supplementation at 32 weeks PMA and used higher limits than planned by SUPPORT. Our proposal is novel in that randomization to the two oxygen strategies begins at birth and continues for as long as the infants are in supplemental oxygen - by implementing this secondary we will be able to determine the impact of these strategies on short and long-term growth.

Methods:

Anthropometric Measures – at birth, postnatal days 7, 14, 21, and 28 days, 32 w PMA and 36 w PMA or discharge (wt, length, HC)

1. Weight - using standard digital electronic scales (c/o infant's nurse)
2. Length - using the Premie Length Board (average of two values, c/o research staff)
3. Head circumference - using paper measurement tape (average of c/o research staff)

Clinical Data-

1. Date when infant regains birth weight
2. Date of first enteral feed
3. Date of full enteral feeds (enteral > 120ml/kg/d)
4. Total number of days on parenteral nutrition
5. 24 h intake 'snapshots' (Parenteral, Enteral) – postnatal days 7, 14, 21, and 28, 32w PMA, 36w PMA or discharge (whichever comes first)
6. Presence of BPD

Intervention Data –

1. Duration of time spent in target saturation ranges of interest (Already part of SUPPORT‡)
2. Median values for unmasked oxygen saturation while still on supplemental oxygen therapy‡
3. Highest daily FiO_2‡
4. Duration of supplemental oxygen exposure‡
5. Documentation of post-discharge oxygen use

Follow Up data –

1. Anthropometric measurements at 18-22months corrected age
2. Neuro-developmental follow up at 18-22 months corrected age

Primary Outcome:

Growth in-hospital and at 18-22 months corrected age and in-hospital growth trajectories in high and low saturation arms.

Sample Size:

Given the importance of using an RCT to establish the impact of different levels of oxygen saturation from birth on short and long term growth, and recognizing the wealth of oxygen saturation data that will be available for analysis combined with the absence of comparable data in the literature, all infants in the SUPPORT Trial should be recruited into this secondary (n=1320). This sample size will be adequate to detect subtle differences in growth between the two groups with adequate ($\geq$80%) power. For example, this sample size will have at least 80% power to detect a difference in means between the two saturation groups of less than 40 g (assuming a mean weight of 1000 g in the control group and a standard deviation of 250 g) using a two group t-test with a 0.05 two-sided significance level.

Statistical Analysis:

Based upon intent-to-treat, differences between treatment arms with respect to continuous outcomes (such as weight, length, etc.) will be assessed by the Student t-test or the Mann-Whitney U-test, depending upon whether the empirical distribution of the data is approximately normal or heavily skewed. Adjusted analyses will be conducted using linear regression to determine the relationship between measures of oxygen saturation and growth in the presence of covariates and confounders (such as site, gestational age, gender, etc.). Categorical outcomes (such as BPD, growth failure, etc.) will be compared across treatment groups using the chi-square test. Logistic regression models will be developed to determine whether oxygen saturation independently affects growth after correction for confounding variables that also alter growth.

In-hospital growth data will be available over multiple points in time. Outcomes available from this temporal distribution will enable us to perform a longitudinal analysis comparing the trajectories of growth between the two treatment groups. Longitudinal studies are powerful both in terms of explanatory power and statistical efficiency. They are useful in examining whether children in the two different oxygen saturation arms have different developmental trajectories over time. Further, longitudinal studies are statistically more efficient since they acknowledge and account for naturally occurring differences among children, including unmeasured characteristics such as genetic make-up, prenatal exposures, etc.

In order to analyze longitudinal growth data we propose to use hierarchical modeling, where the first stage models growth as a function of time/child's age, and the second stage models this association as a function of each child's

treatment status. This flexible modeling formulation allows each child to have its own unique developmental trajectory, which could depend on its treatment status.

Discussion of Anticipated Results

We anticipate a better growth outcome in-hospital and at 18-22 months corrected age in the infants randomized to the lower target saturation range who maintained their median oxygen saturations within study range. We further anticipate that longitudinal analyses will demonstrate that these infants will have a sustained higher trajectory of growth over time compared to infants in the higher target saturation range.

Budget:

Additional nursing time, needed to collect required anthropometric data and other data from chart review at discharge and at follow-up, is estimated to be 1 hour. The cost for the entire cohort (1320 subjects), at $32.00 per nursing hour, would be $42,220. Assuming a 35% mortality for this extremely preterm population (estimated from GDB), 858 subjects could be expected to survive to discharge and estimating time for survivors alone will reduce the budget to $27,456.00.

References:

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Askie LM, Henderon-Smart DJ. Cochrane Review "Restricted versus liberal exposure for preventing morbidity and mortality in preterm or low birth weight infants", last updated October 2003.

Baraldi E, Carra S, Vencato F, Filippone M, et al. Home oxygen therapy in infants with BPD: a prospective study. Eur J Pediatr 1997; 156: 878-882

Berry MA, Abrahamowicz M, Usher R. Factors associated with growth of extremely premature infants during initial hospitalization. Pediatrics 1997; 100: 640-646

Cooke RJ, Ainsworth SB, Fenton AC. Postnatal growth retardation: a universal problem in preterm infants. Arch Dis Child Fetal Neonatal Ed 2004; 89: F428-F430

Dundar B, Akcoral A, Saylam G, et al. Chronic hypoxemia leads to reduced serum IGF-1 levels in cyanotic congenital heart disease. J Pediatr Endocrinol Metab 2000; 13: 431-436

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with BPD. Am J Dis Child 1987; 141: 992-5

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Lemons JA, Bauer CR, et al for NICHD Neonatal Research Network. Very low birth weight outcomes of the National Institute of Child Health and Development Neonatal Research Network, January 1995 through December 1996. Pediatrics 2001; 107(1)

Markestad T, Fitzhardinge PM: Growth and development in children recovering from BPD. J Pediatr 1981;98:597-602

Mortola JP, Xu L, Lauzon A-M. Body growth, lung and heart weight, and DNA content in newborn rates exposed to different levels of chronic hypoxia. Can J Physiol Pharmacol 1990; 68: 1590-1594

Moyer-Mileur LJ, DW Nielson, KD Pfeffer, MK Witte and DL Chapman. Eliminating sleep-associated hypoxemia improves growth in infants with bronchopulmonary dysplasia. Pediatrics, Oct 1996; 98: 779 – 783

Singhal A, Cole TJ, Fewtrell M, Deanfield J, Lucas A. Is slower early growth beneficial for long-term cardiovascular health? Circulation 2004; 109: 1108-1113

The STOP-ROP Multicenter Study Group. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics 2000; 105:295-310

Tin W, Milligan DWA, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001; 84: F106-110

This form should be completed on day of life 1, 7, 14, 21 and 28, corrected ages 32weeks and 36weeks or discharge.

1. Date: __ __ /__ __ /__ __ __ __ (Month / Day / Year) **2. Day of Life:** __ __ __

3. Today's New Weight (gms): __ __ __ __

4. Today's New Length (cm): __ __ . __

5. Today's New Head Circumference (cm): __ __ . __

A. PARENTERALNUTRITIONAL INTAKE

1. Was there parenteral Intake? Y N

If Yes,

2. PN	**% Dextrose**	**AA Ordered (gm/kg/d)**	**PN Volume Received (cc's)**	**% Lipid Solution**	**Intralipid Volume Received (cc's)**
a. Today's 1st Bag	__ __ . __	__ . __	__ __ __ . __	__ __	__ __ . __
b . Today's 2nd Bag	__ __ . __	__ . __	__ __ __ . __	__ __	__ __ . __
c. Today's 3rd Bag	__ __ . __	__ . __	__ __ __ . __	__ __	__ __ . __

B. ENTERAL INTAKE

1. Was there enteral Intake? Y N

a. If Yes, record information below:

	Type	**Caloric Density (Kcal/ounce)**	**Volume Received (cc's)**	**Nutrient Additives**
1.	__ __ __	__ __	__ __ __ . __	__ __ __ __
2.	__ __ __	__ __	__ __ __ . __	__ __ __ __
3.	__ __ __	__ __	__ __ __ . __	__ __ __ __
4.	__ __ __	__ __	__ __ __ . __	__ __ __ __

Enteral Nutrition Key

Type:	Nutrient Additives:
00= none 01= breast milk (full strength) 02= Similac Special Care 03= Enfamil Premature Formula 04= Similac (regular term infant formula) 05= Enfamil (regular term infant formula) 06= Pregestimil 07= Nutramigen 08= Alimentum 09= Prosobee 10= Isomil 11= Similac 60/40 12= Similac Natural Care 13= Neosure 14= Enfamil 22 15= Other 16= Pedialyte	2= MCT or other oil 4= polycose 6= human milk fortifier 8= formula powder or liquid 9= Promod 7= other

Initials of person completing this form ___

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: support protocol for parent
Date: Monday, October 24, 2005 2:46:16 PM

(b) (6). Enough said.
wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 24, 2005 11:34 AM
To: wrich@ucsd.edu
Subject: Re: support protocol for parent

Wade
Sorry for the delay as I am travelling . You may share the protocol with the parents. Do they have a medical baxkground?

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wade Rich <wrich@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Mon Oct 24 12:08:27 2005
Subject: support protocol for parent

Rose,
Can I provide the protocol for SUPPORT to an parent or grandparent? I know some of the
info is posted on trials.gov., but the full protocol is not so I wanted to make sure of the regs. Neil is in-flight, which is why I am asking you.

Wade

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT Growth secondary
Date: Monday, October 24, 2005 2:26:47 PM
Attachments: growthprot revised Aug 9 2005.doc

Hi Rose,
Would you like me to send out the draft protocol as well as the form for the Growth secondary when I send out the scheduled conference call?
Thanks
--see attached

Kristin Zaterka-Baxter
RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study: A Proposed Secondary Study

Cristina Navarrete MD, and Shahnaz Duara MD
University of Miami Miller School of Medicine, Miami, FL.

Abstract:

Post-natal growth restriction is a major problem in preterm infants. Perturbations in oxygenation are recognized to influence post-natal growth; hypoxic conditions can directly impair growth and hyperoxic conditions predispose infants to BPD, which in turn has been linked to poor growth. The NICHD Neonatal Network is conducting a prospective trial of preterm infants randomized to two levels of baseline oxygen saturations. The effect of baseline saturations on pulmonary morbidity and ROP are the primary outcome measures. With respect to post-natal growth, there is a paucity of data relating alterations in baseline oxygen saturation and/or frequent deviations above or below the baseline to growth outcomes. We propose a secondary study to quantify short-term growth velocity in-hospital and long-term growth at 18-22 months of corrected age for infants enrolled in the SUPPORT Trial in relationship to oxygen saturation.

A. Hypothesis to be tested

Primary:

1. Infants in the low oxygen saturation group (85-89%) will have better in-hospital and long-term (18-22 months corrected age) growth.

2. Trajectories of growth in hospital will be better for infants in the low oxygen saturation group.

Secondary:

1. Growth will be greater in infants who spend > 50% of the time with daily median oxygen saturation between 85% -95% while on supplemental oxygen, independent of randomization to low or high oxygen saturation.

2. Infants with BPD will have poorer in-hospital and long-term growth than infants without BPD, independent of the saturation randomization arm.

3. Better long-term growth will be positively related to neuro-developmental outcome, independent of the saturation randomization arm.

B. Specific Aims:

1. To determine anthropometric measurements (wt, HC, length) in infants randomized to low and high oxygen saturation arms, from birth to hospital discharge and again at 18-22 months corrected age.
2. To determine nutritional intake (parenteral and enteral) during hospital stay.
3. To determine the percentage of infants with growth <10 percentile at 36 weeks PMA or discharge, whichever comes first.
4. To determine the percentage of infants with growth <10 percentile at 18-22 months corrected age.
5. To determine growth in relation to the proportion of time spent with oxygen saturation
    a. <85% and >95%
    b. 85%-95%
6. To determine growth in relation to infants' median oxygen saturation while in supplemental oxygen
    a. median oxygen saturation > 95%
    b. median oxygen saturation 85% - 95%
    c. median oxygen saturation < 85%
7. To relate incidence of BPD in low and high saturation arms to growth.
8. To determine in-hospital growth velocity/trajectory in low and high saturation arms.
9. To determine long-term growth velocity/trajectory, from hospital discharge to follow up at 18-22 months corrected age in low and high saturation arms.
10. To relate neuro-developmental outcome at 18-22 months corrected age to long-term growth in low and high saturation arms.

Rationale:

The SUPPORT Trial will randomize infants to two ranges of SpO2 in order to test the hypothesis that use of a lower SpO2 range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity and/or the need for surgical intervention. Retrospective cohort data from several units in the U.K., with different oxygen supplementation policies, revealed poorer growth patterns in the preterm infants exposed to higher oxygen saturations for the duration of oxygen exposure (Tin 2001). Conversely, observational data of infants with established BPD show better growth with home oxygen support (Groothius 1987), and two recent RCT of different target saturations in older oxygen-dependent premature infants showed no difference in short or long-term growth outcomes (STOP-ROP 2000, BOOST Trial 2003). There are no RCT data evaluating the short or long-term growth impact of different SpO2 strategies with supplemental oxygen use in a birth cohort of extremely preterm infants. Therefore, this study provides an opportunity for us to

obtain critically needed growth information on premature infants who are exposed from birth to different target oxygen saturation strategies.

Background

Improvements in antenatal care, respiratory support and nutrition have contributed to increased survival of ELBW infants. As the number of survivors increase, the long term outcome of these infants becomes more important. Lemons et al described growth failure or weight <10th percentile at 36 weeks postmenstrual age in 97% of ELBW infants surviving to discharge. Some morbidities in adulthood are linked to growth during the early post-natal period (Singhal 2004) and make adequacy of growth in this population of heightened interest.

Instead of following intra-uterine growth curves of age matched fetuses, VLBW infants exhibit wide-spread post-natal growth retardation (Cooke 2004), losing ground during the first weeks of life (Berry 1997). To resume growth post-natally, nutrition is of paramount importance; however, other factors such as severity of illness and perhaps oxygenation also play a role. Observational studies of infants with BPD showed poor post-natal growth when infants were sent home without oxygen supplementation (Markestad 1981).

Although preterm infants without lung disease attain oxygen saturations >95%, artificial attempts to keep arterial oxygenation at a "physiological" level may not be beneficial to growth, the lung or retina (Tin 2001). Animal studies have shown that newborn mammals (mice, rats, guinea pigs) develop poor growth with chronic hypoxia and that blunted body growth is directly proportional to the profundity of the exposure to chronic hypoxia (Mortola 1990). Chronic hypoxemia has also been suggested as the cause of poor growth in patients with cyanotic congenital heart disease (Dundar 2000). When home oxygen supplementation was discontinued inappropriately by parents in a cohort of VLBW infants with BPD, there was a deceleration in the rate of weight gain, which improved when oxygen supplementation was resumed (Groothius 1987). Hudak et al in 1989 observed that ELBW infants with CLD who went home on oxygen supplementation had good catch-up growth at 19 months. Taken collectively, these data suggest that hypoxic conditions affect growth negatively and supplementing oxygen may improve growth.

The optimal level of oxygen saturation to promote post-natal growth is unknown. Most of the available human data is limited to oxygen supplementation of infants who are oxygen dependent or have BPD. Baraldi et al demonstrated that discharged infants with BPD, who were kept on supplemental oxygen to keep saturations above 94%, had progressive but poor weight gain (stayed below 3rd percentile) at 9 months corrected age follow-up. In infants with BPD whose oxygen supplementation was intentionally discontinued, the subset who exhibited episodes of desaturations below 88-91% had a significant decline in the rate of weight gain as compared to those who maintained saturations above 92% (Moyer-Mileur 1996). Conversely, when two different oxygen saturation control policies (high: 88-98% and low: 70-90%) were retrospectively reviewed in <28

week gestation infants, the infants being cared for in the high oxygen saturation policy units were more likely to weigh less than the 3rd percentile at discharge (45% vs. 17%, Tin 2001). The infants assigned to the high oxygen saturation limits were also more likely to have BPD and ROP.

Recently, the BOOST Trial demonstrated that randomizing infants born <30 weeks gestation who were still on oxygen at 32 weeks postmenstrual age either to standard saturations (91-94%) or to high saturations (95-98%) produced no significant difference in growth at 12 months corrected age. This study, while randomizing infants to two different levels of saturations (conventional and high), only enrolled infants if they were still on oxygen supplementation at 32 weeks PMA and used higher limits than planned by SUPPORT. Our proposal is novel in that randomization to the two oxygen strategies begins at birth and continues for as long as the infants are in supplemental oxygen - by implementing this secondary we will be able to determine the impact of these strategies on short and long-term growth.

Methods:

Anthropometric Measures – at birth, postnatal days 7, 14, 21, and 28 days, 32 w PMA and 36 w PMA or discharge (wt, length, HC)

1. Weight - using standard digital electronic scales (c/o infant's nurse)
2. Length - using the Premie Length Board (average of two values, c/o research staff)
3. Head circumference - using paper measurement tape (average of c/o research staff)

Clinical Data-

1. Date when infant regains birth weight
2. Date of first enteral feed
3. Date of full enteral feeds (enteral > 120ml/kg/d)
4. Total number of days on parenteral nutrition
5. 24 h intake 'snapshots' (Parenteral, Enteral) – postnatal days 7, 14, 21, and 28, 32w PMA, 36w PMA or discharge (whichever comes first)
6. Presence of BPD

Intervention Data –

1. Duration of time spent in target saturation ranges of interest (Already part of SUPPORT‡)
2. Median values for unmasked oxygen saturation while still on supplemental oxygen therapy‡
3. Highest daily FiO_2‡
4. Duration of supplemental oxygen exposure‡
5. Documentation of post-discharge oxygen use

Follow Up data –

1. Anthropometric measurements at 18-22months corrected age
2. Neuro-developmental follow up at 18-22 months corrected age

Primary Outcome:

Growth in-hospital and at 18-22 months corrected age and in-hospital growth trajectories in high and low saturation arms.

Sample Size:

Given the importance of using an RCT to establish the impact of different levels of oxygen saturation from birth on short and long term growth, and recognizing the wealth of oxygen saturation data that will be available for analysis combined with the absence of comparable data in the literature, all infants in the SUPPORT Trial should be recruited into this secondary (n=1320). This sample size will be adequate to detect subtle differences in growth between the two groups with adequate ($\geq$80%) power. For example, this sample size will have at least 80% power to detect a difference in means between the two saturation groups of less than 40 g (assuming a mean weight of 1000 g in the control group and a standard deviation of 250 g) using a two group t-test with a 0.05 two-sided significance level.

Statistical Analysis:

Based upon intent-to-treat, differences between treatment arms with respect to continuous outcomes (such as weight, length, etc.) will be assessed by the Student t-test or the Mann-Whitney U-test, depending upon whether the empirical distribution of the data is approximately normal or heavily skewed. Adjusted analyses will be conducted using linear regression to determine the relationship between measures of oxygen saturation and growth in the presence of covariates and confounders (such as site, gestational age, gender, etc.). Categorical outcomes (such as BPD, growth failure, etc.) will be compared across treatment groups using the chi-square test. Logistic regression models will be developed to determine whether oxygen saturation independently affects growth after correction for confounding variables that also alter growth.

In-hospital growth data will be available over multiple points in time. Outcomes available from this temporal distribution will enable us to perform a longitudinal analysis comparing the trajectories of growth between the two treatment groups. Longitudinal studies are powerful both in terms of explanatory power and statistical efficiency. They are useful in examining whether children in the two different oxygen saturation arms have different developmental trajectories over time. Further, longitudinal studies are statistically more efficient since they acknowledge and account for naturally occurring differences among children, including unmeasured characteristics such as genetic make-up, prenatal exposures, etc.

In order to analyze longitudinal growth data we propose to use hierarchical modeling, where the first stage models growth as a function of time/child's age, and the second stage models this association as a function of each child's

treatment status. This flexible modeling formulation allows each child to have its own unique developmental trajectory, which could depend on its treatment status.

Discussion of Anticipated Results

We anticipate a better growth outcome in-hospital and at 18-22 months corrected age in the infants randomized to the lower target saturation range who maintained their median oxygen saturations within study range. We further anticipate that longitudinal analyses will demonstrate that these infants will have a sustained higher trajectory of growth over time compared to infants in the higher target saturation range.

Budget:

Additional nursing time, needed to collect required anthropometric data and other data from chart review at discharge and at follow-up, is estimated to be 1 hour. The cost for the entire cohort (1320 subjects), at $32.00 per nursing hour, would be $42,220. Assuming a 35% mortality for this extremely preterm population (estimated from GDB), 858 subjects could be expected to survive to discharge and estimating time for survivors alone will reduce the budget to $27,456.00.

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Singhal A, Cole TJ, Fewtrell M, Deanfield J, Lucas A. Is slower early growth beneficial for long-term cardiovascular health? Circulation 2004; 109: 1108-1113

The STOP-ROP Multicenter Study Group. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics 2000; 105:295-310

Tin W, Milligan DWA, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001; 84: F106-110

From: Zaterka-Baxter, Kristin
To: sduara@miami.edu; richard.ehrenkranz@yale.edu; bpoindex@iupui.edu; Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Hastings, Betty J.; Petrie, Carolyn
Subject: SUPPORT Growth Secondary Study
Date: Wednesday, October 19, 2005 11:23:56 AM
Attachments: GRO-01 [Nutrition Data].doc

Dear All

Please send me your availability for a conference call to discuuss the SUPPORT secondary study. Attached for your review is the Nutritional Intake Form (GRO-01)

Monday Oct. 24
Tuesday Oct. 25
Wednesday Oct. 26
Thursday Oct. 27
Friday Oct. 28

Monday Oct. 31
Tuesday Nov. 1
Wednesday Nov. 2
Thursday Nov. 3
Friday Nov. 4

Monday Nov. 7
Tuesday Nov. 8
Wednassday Nov. 9
Thursday Nov. 10
Friday Nov. 11

Thanks,
Kris

Kristin Zaterka-Baxter
RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

This form should be completed on day of life 1, 7, 14, 21 and 28, corrected ages 32weeks and 36weeks or discharge.

1. Date: __ __ / __ __ / __ __ __ __ (Month / Day / Year) **2. Day of Life:** __ __ __

3. Today's New Weight (gms): __ __ __ __

4. Today's New Length (cm): __ __ . __

5. Today's New Head Circumference (cm): __ __ . __

A. PARENTERALNUTRITIONAL INTAKE

1. Was there parenteral Intake? Y N

If Yes,

2. PN	**% Dextrose**	**AA Ordered (gm/kg/d)**	**PN Volume Received (cc's)**	**% Lipid Solution**	**Intralipid Volume Received (cc's)**
a. Today's 1st Bag	__ __ . __	__ . __	__ __ __ . __	__ __	__ __ . __
b . Today's 2nd Bag	__ __ . __	__ . __	__ __ __ . __	__ __	__ __ . __
c. Today's 3rd Bag	__ __ . __	__ . __	__ __ __ . __	__ __	__ __ . __

B. ENTERAL INTAKE

1. Was there enteral Intake? Y N

a. If Yes, record information below:

	Type	**Caloric Density (Kcal/ounce)**	**Volume Received (cc's)**	**Nutrient Additives**
1.	__ __ __	__ __	__ __ __ . __	__ __ __ __
2.	__ __ __	__ __	__ __ __ . __	__ __ __ __
3.	__ __ __	__ __	__ __ __ . __	__ __ __ __
4.	__ __ __	__ __	__ __ __ . __	__ __ __ __

Enteral Nutrition Key

Type:	Nutrient Additives:
00= none 01= breast milk (full strength) 02= Similac Special Care 03= Enfamil Premature Formula 04= Similac (regular term infant formula) 05= Enfamil (regular term infant formula) 06= Pregestimil 07= Nutramigen 08= Alimentum 09= Prosobee 10= Isomil 11= Similac 60/40 12= Similac Natural Care 13= Neosure 14= Enfamil 22 15= Other 16= Pedialyte	2= MCT or other oil 4= polycose 6= human milk fortifier 8= formula powder or liquid 9= Promod 7= other

Initials of person completing this form ___

From:	Roy Heyne
To:	drfjcmd@aol.com; steichji@email.uc.edu; adusick@iupui.edu; Higgins, Rosemary (NIH/NICHD) [E]; golds005@mc.duke.edu; apappas@med.wayne.edu; sshankar@med.wayne.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; MPeralta@peds.uab.edu; newman@rti.org; srhintz@stanford.edu; yvaucher@ucsd.edu; gary_myers@urmc.rochester.edu; Timothy_Stevens@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; rdillard@wfubmc.edu; bvohr@wihri.org; richard.ehrenkranz@yale.edu
Cc:	JACKIE Hickman; bss5@cwru.edu; dkennedy@dmc.org; ldrichar@iupui.edu; mbball@leland.stanford.edu; lohme001@mc.duke.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; SEguaras@med.miami.edu; ellen_hale@oz.ped.emory.edu; VPhillips@peds.uab.edu; adas@rti.org; bkh@rti.org; Teresa.Gratton@uc.edu; mgfuller@ucsd.edu; diane_hust@urmc.rochester.edu; maegan.c.currence@uth.tmc.edu; bjacksn@wfubmc.edu; lnoel@wihri.org; elaine.romano@yale.edu
Subject:	Re: Please Review: SUPPORT Follow-up MOO and Forms
Date:	Monday, October 17, 2005 6:29:11 PM

My comments on the manual and forms are as follows:

1-2 Section 1.5: NICU Discharge: Though this is covered in more detail on 7-1, would suggest inserting after "prior to NICU discharge" the following: "or within 30 days post discharge"

For 6 and 12 month interviews, would suggest deleting "telephone" and then adding "by telephone or face-to-face" (as specified on 2-6 and 5-2).

2-5 Section 2.3.3 I don't have a problem encouraging families to use the diaries, but I think it unrealistic to expect the average family we deal with to keep it up over a period of 6 months with any degree of consistency/completeness. Granted whatever they do record may bolster 6 month recall, but I don't think we should only ask them to report what they have recorded, unless they are confident that it is complete.

3-1 Section 3.3 Though the amount of text added to the main SUPPORT consent form to include the follow-up study is modest, and the follow-up design is not complicated, the main trial is more involved, and I suspect it may be all some parents can do to understand and consent to the main trial, especially at the time sensitive point the main trial consent needs to be obtained. Not to mention the fact that a not insignificant percent of the smallest infants may not survive. Though it would be nice to get it all out of the way up front, I think someone will still need to rediscuss the follow-up study closer to discharge or shortly therafter.

5-2 Discharge The questionnaire in Appendix B actually comprises 25 questions, some of which are multi-part. The first 6 are demographic, 11 concern home environment, 2 relate to diet, 1 provides alternate contact info, and a separate 5 cover family history (also multipart). The description here should reflect that.

Likewise, the 6 and 12 month questionnaires comprise a total of 27 questions (again, some mult-part); and the 18-22 month form includes those 27 plus another 7 concerning 1 year history of infection/allergy.

5-3 Section 5.4 Might want to cross-reference 7-1 with regards to the definition of "windows" for each of the questionnaires.

7-2 Intro The second paragraph of the intro script indicates "it may be helpful if you could gather...." This suggests that some interviews may proceed without the requested items, if, for example diary cannot be found or has not been kept, or if meds are not readily available at the time of the call. Though it might be of some interest to ask/note whether and to what extent the answers are based on pure recall vs. diary (or medication containers), I'm not sure how one would meaningfully use that info to characterize/qualify results.

7-3 Question 6-8 Since the symptom of wheezing is included in these 3 utilization questions, the definition of

wheezing and audio clip really needs to be introduced prior to these questions; alternatively, 6-8 could be moved down to follow 9-15.

7-5 Q. 9e1-9f2 Do these questions literally refer to the last 6 months, or should they, like 6-8, be limited to the period since the last contact? Same for Q. 11-12.

7-7 Q. 11-12 Secondly, I think averaging over 6 months will be a challenge except in the case of the child with relatively infrequent, or conversely frequent, sx.

7-7 Q. 10c It is not clear what kind/duration of cough "the cough" refers to. Are we really interested in the first time the child had a 3-4 day URI associated cough?

Or are we more interested in the first month the child had a cough without cold, that persisted more than a few days?

7-7 Q. 12 Typo: "...change your (not for) daytime or evening plans...."

7-11 Q. 26 Might want to note that "pure oxygen is 100%"

8-1 Actually,questions 28-29 are not principally about allergies, but about upper or lower respiratory tract infections. Would suggest a separate intro for these 2 questions, since the allergy intro might mislead the parent in answering 28-29.

Appendix C C-2 The last paragraph under Procedures needs to be omitted, since we are dropping the chart audit.

C-6 the first sentence of the last paragraph adds language about "wheezing in the first 2 years" but does not mention "coughing"

Appendix E Breathing Diary Blank. See comments above re diary.

Appendix B 6, 12, 18-22 month questionnaires:

Questions 9e-f; 10e-f: There is a big difference between never and twice a week for daytime, but if that's the key threshold we are interested in, fine.

Question 13: As I mentioned at our last meeting, I think this question is going to miss those infants whose physicians continue to carry them under the NICU discharge diagnosis of BPD/CLD, in which case future events are considered "flare-ups" of that chronic disease, rather than just "reactive airway disease" or "asthma" variants, which should only be applied if there is evidence to support that alternate/additional diagnosis.

Thus I would still recommend including BPD/CLD or flare-ups thereof in question 13, assuming we don't need/want to separate it out as a separate question.

Question 27: Since all of the meds in the first column of the table can be inhaled, I would modify the label for Intal and Tilade "Other Inhaled Medications"

Prednisolone is not included in your list of systemic steroids.

Finally, has the protocol been modified to reflect certain key changes in questionnaire administration (such as possibility of face to face and windows for admin); and to reflect omission of the outpatient chart review, since it is the protocol and consents that we submit to IRB, rather than manual of ops. There is also one table in the protocol (Table 1 on page 8), which lists Important Covariates, which I don't think has been updated to reflect streamlining of the questionnaires, since the current questionnaires no longer ascertain info in the Environmental category regarding urban vs rural residence, presence of dust; nor either of the listed Health Services parameters, as far as I can tell; nor info re GERD or congenital anatomic airway abnormalities (unless these were diagnosed and captured in the NICU).

>>> "Newman, Jamie" <newman@rti.org> 10/13/05 4:17 PM >>>
Dear Follow-up PIs and Coordinators,

Attached are the SUPPORT Follow-up Manual of Operations and questionnaires for your review and comments.

The agenda for the next Coordinators' call on Thurs 10/20 has already been set though we would very much like your comments.

It has been difficult finding a day/time that fits the PI's schedules so we are expanding the date/time options. Please let me know your availability for these additional times:

Thursday, October 20: afternoon

Friday, October 21: 12-3

Monday, October 31: 4-5pm

Tuesday, Nov 1: afternoon

Wednesday Nov 2: afternoon

Thurs Nov 3 afternoon

Friday Nov 4 afternoon

Thank you,

Jamie E. Newman, MPH

Statistics Research Division

RTI International

Telephone: (919) 485-5719

Fax: (919) 485-7762

newman@rti.org

From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Please Review: SUPPORT Follow-up MOO and Forms
Date: Monday, October 17, 2005 11:01:55 AM

Rose
Thanks
Seetha

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 17, 2005 9:30 AM
To: Shankaran, Seetha
Subject: RE: Please Review: SUPPORT Follow-up MOO and Forms

It sounds likes we need a call with them in the next 2-3 weeks. I will have Jamie Newman set it up.

Thanks
Rose

From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Monday, October 17, 2005 9:23 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: FW: Please Review: SUPPORT Follow-up MOO and Forms

Rose
When we do get the Follow-up PI's on a call can I add 2 items to agenda
a) Revised Extended Follow -UP study of Hypothermia subjects (will send out the additions of NEPSY/deletions Beery, VMI)
b) Minor change in aEEG FU form (to ensure that the "untestable" children are coded correctly and not as "missing"
What do you think
Let me know
Thanks
Seetha

-----Original Message-----
From: Betty Vohr [mailto:BVohr@WIHRI.org]
Sent: Saturday, October 15, 2005 2:50 PM
To: Newman, Jamie; Stevens, Timothy; Higgins, Rosemary (NIH/NICHD); Shankaran, Seetha; richard.ehrenkranz@yale.edu; jon.e.tyson@uth.tmc.edu; MPeralta@PEDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; Pappas, Athina; Shankaran, Seetha; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; rdillard@wfubmc.edu; gary_myers@URMC.Rochester.edu; adusick@iupui.edu; steichjj@email.uc.edu; (b) (6)
Cc: maegan.c.currence@uth.tmc.edu; SEguaras@med.miami.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; Janet.Morgan@childrens.com; VPhillips@PEDS.UAB.EDU; mgfuller@ucsd.edu; Lucy Noel; ldrichar@iupui.edu; lohme001@mc.duke.edu; bjacksn@wfubmc.edu; diane_hust@URMC.Rochester.edu; mbball@leland.stanford.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; ellen_hale@oz.ped.emory.edu; Kennedy, Deborah (DMC); Jackie.Hickman@childrens.com; bss5@cwru.edu; Das, Abhik; Hastings, Betty J.
Subject: RE: Please Review: SUPPORT Follow-up MOO and Forms

I have a few comments for the conference call.

1. In the directions on page 1 I would change it to administered by trained study staff to the parent/guardian. At the moment it states a nurse and some of the IRBs might have a problem if a physician or other trained professional(respiratory therapist) administered the questionnaire.

2. The breathing diary was not forwarded. There was nothing in Appendix E. ?

3. The questionnaires need to have a place on each page to put the study number as an identifier.

4. The parent name is requested on the form. This conflicts with current confidentiality requirements. I believe that the code is adequate.

5. Family history form for maternal and paternal grandparents. How is this to be filled out if the person has expired,or if the person being interviewed does not have the information ?

6. Linda Mayes is not the Follow-up PI at Yale, it is Richard Ehrenkranz.

From: Newman, Jamie [mailto:newman@rti.org]
Sent: Thu 10/13/2005 5:17 PM
To: Stevens, Timothy; Higgins, Rosemary (NIH/NICHD); sshankar@med.wayne.edu; richard.ehrenkranz@yale.edu; jon.e.tyson@uth.tmc.edu; MPeralta@PEDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; apappas@med.wayne.edu; sshankar@med.wayne.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; rdillard@wfubmc.edu; gary_myers@urmc.rochester.edu; Betty Vohr; adusick@iupui.edu; steichjj@email.uc.edu; (b) (6)
Cc: maegan.c.currence@uth.tmc.edu; SEguaras@med.miami.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; Janet.Morgan@childrens.com; VPhillips@peds.uab.edu; mgfuller@ucsd.edu; Lucy Noel; ldrichar@iupui.edu; lohme001@mc.duke.edu; bjacksn@wfubmc.edu; diane_hust@urmc.rochester.edu; mbball@leland.stanford.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; ellen_hale@oz.ped.emory.edu; dkennedy@dmc.org; Jackie.Hickman@Childrens.com; bss5@cwru.edu; Das, Abhik; Hastings, Betty J.
Subject: Please Review: SUPPORT Follow-up MOO and Forms

Dear Follow-up PIs and Coordinators,
Attached are the SUPPORT Follow-up Manual of Operations and questionnaires for your review and comments.

The agenda for the next Coordinators' call on Thurs 10/20 has already been set though we would very much like your comments.

It has been difficult finding a day/time that fits the PI's schedules so we are expanding the date/time options. Please let me know your availability for these additional times:

Thursday, October 20: afternoon
Friday, October 21: 12-3
Monday, October 31: 4-5pm
Tuesday, Nov 1: afternoon
Wednesday Nov 2: afternoon
Thurs Nov 3 afternoon
Friday Nov 4 afternoon

Thank you,

Jamie E. Newman, MPH
Statistics Research Division
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Newman, Jamie
To: Stevens, Timothy; Higgins, Rosemary (NIH/NICHD) [E]; sshankar@med.wayne.edu; richard.ehrenkranz@yale.edu; jon.e.tyson@uth.tmc.edu; MPeralta@PEDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; apappas@med.wayne.edu; sshankar@med.wayne.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; rdillard@wfubmc.edu; gary_myers@urmc.rochester.edu; bvohr@wihri.org; adusick@iupui.edu; steichij@email.uc.edu (b) (6)
Cc: maegan.c.currence@uth.tmc.edu; SEguaras@med.miami.edu; MNeri@med.miami.edu; Reverett@med.miami.edu; Janet.Morgan@childrens.com; VPhillips@peds.uab.edu; mgfuller@ucsd.edu; lnoel@wihri.org; ldrichar@iupui.edu; lohme001@mc.duke.edu; bjacksn@wfubmc.edu; diane_hust@urmc.rochester.edu; mbball@leland.stanford.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; ellen_hale@oz.ped.emory.edu; dkennedy@dmc.org; Jackie.Hickman@Childrens.com; bss5@cwru.edu; Das, Abhik; Hastings, Betty J.
Subject: Please Review: SUPPORT Follow-up MOO and Forms
Date: Thursday, October 13, 2005 5:17:40 PM
Attachments: SUPPORTFUMOOdraft10-12.doc
SUPPORT FU Forms10_12.doc

Dear Follow-up PIs and Coordinators,
Attached are the SUPPORT Follow-up Manual of Operations and questionnaires for your review and comments.

The agenda for the next Coordinators' call on Thurs 10/20 has already been set though we would very much like your comments.

It has been difficult finding a day/time that fits the PI's schedules so we are expanding the date/time options. Please let me know your availability for these additional times:

Thursday, October 20: afternoon
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Thank you,

Jamie E. Newman, MPH
Statistics Research Division
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

SUPPORT Trial
Pulmonary Outcomes Follow-up Study

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial)

NICHD Neonatal Research Network

Manual of Operations

October 12, 2005

TABLE OF CONTENTS

Chapter 1
Overview and Trial Design

1.1 Introduction

This manual provides detailed instructions of study procedures for the Follow-up Study of the NICHD SUPPORT Trial Pulmonary Outcomes Follow-up Study (The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants). This manual should be used as a reference guide for study staff including investigators, coordinators, and data managers. The trial objectives and design are summarized briefly below. For further discussion to the study background and design, please refer to the Follow-up Study Protocol.

1.2 Study Design

This study is a longitudinal follow-up of surviving infants enrolled, randomized and treated as part of the SUPPORT Trial, which was a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This follow-up study will determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the incidence of symptomatic airway dysfunction (defined as recurrent wheezing or chronic cough) and volume of outpatient care in the first 18-22 months' corrected age (CA). The individual factors to be tested in this follow-up study are:

1) Symptomatic airway dysfunction and need for outpatient pulmonary care in the first 18-22 months among infants managed with a lower SpO2 range (85% to 89%) as compared to a higher, more conventional SpO2 range (91% to 95%).

2) Symptomatic airway dysfunction and need for outpatient pulmonary care in the first 18-22 months corrected age among infants managed with CPAP and a permissive ventilatory strategy versus infants managed with prophylactic surfactant and conventional ventilation begun in the delivery room and continuing in the NICU.

Table 1 below describes the study treatment groups. Refer to the SUPPORT Trial Protocol for further details regarding the projected outcomes relative to the study interventions

Table 1: SUPPORT Trial Study Treatment Groups

Randomized Intervention	**Low SpO2 85% to 89%**	**High SpO2 91 to 95%**
Treatment Early CPAP	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control Prophylactic/Early Surfactant	Control + Low SpO2	Control + High SpO2

1.3 Primary Hypotheses

1) We hypothesize that relative to infants managed with a higher SpO2 range (91% to 95%), infants managed with a lower SpO2 range (85% to 89%) will have less frequent episodes of

symptomatic airway dysfunction and reduced need for outpatient pulmonary care at 18-22 months' CA.

2) We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

1.4 Secondary Hypotheses

1) We hypothesize that **among infants with CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

2) We hypothesize that **among infants without CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

1.5 Summary of Data Forms

The following is a summary of the data forms used in this study. Further details on each form are provided in subsequent chapters. A complete set of forms can be found in Appendix A.

NICU Discharge-Baseline Interview (SUPF01)
This interview will be administered to the parent or guardian by a trained study nurse prior to NICU discharge. Questions concerning family medical history, anticipated living arrangements, and alternate contact information will be asked.

The purpose of the discharge questionnaire is to assure adequate randomization of important covariates affecting outpatient respiratory health and to obtain baseline data on home environment and family history of respiratory diseases.

6 Month and 12 Month Interview (SUPF02)
This interview will be administered to the parent or guardian by a trained telephone interviewer at 6 months' CA and again at 12 months' CA.

The purpose of these questionnaires is to obtain an **interval** respiratory history. Questions are designed to collect respiratory history since the last contact with the interviewee, such that when the 6, 12 and 18-22 month questionnaires are taken together, a complete respiratory history over the time period is collected.

18-22 Month Interview (SUPF03)

This interview will be administered to the parent or guardian at 18-22 months CA by either telephone interview prior to the regularly scheduled 18-22 month NICHD developmental follow up clinic visit or face to face at the time of the visit.

The purpose of these questionnaires is to obtain an **interval** respiratory history and to identify environmental exposures that may increase the likelihood of symptomatic airway dysfunction.

Chapter 2
Administration

2.1 Organizational Structure

The NICHD Neonatal Research Network is conducting this study. The Network is funded by the NICHD under cooperative agreements with seventeen institutions comprised of sixteen clinical centers and a data coordinating center. The Steering Committee for the Network consists of the Principal Investigator from each clinical center, the data center, and the NICHD project officer. The Steering Committee Chairman is appointed by NICHD and is not a Principal Investigator from any of the Clinical Centers.

SUPPORT Trial Follow-up Subcommittee

The SUPPORT Protocol Subcommittee is responsible for the preparation and maintenance of the protocol, data forms, and manual of operations. This subcommittee will monitor the overall study performance (including protocol compliance) and will report the progress of the trial to the Steering Committee. SUPPORT Subcommittee members are:

Neil Finer, MD

Waldemar A. Carlo, MD,

Edward F. Donovan MD

Michele Walsh, MD

Shahnaz Duara, MD

Rosemary D. Higgins, MD

Abhik Das, PhD

Ruth Everett, RN

Wade Rich, RRT

In addition, Dr. Vohr, as director of the Follow Up Program, will coordinate input from the Follow Up PIs. Timothy P. Stevens, MD, MPH and Peter Szilagyi, MD, MPH from the Department of Pediatrics at the University of Rochester will be instrumental in designing, implementing and executing the clinical studies outlined here and will have significant ongoing involvement with the project.

2.2 Participating NICHD Neonatal Research Network Centers

Centers from the NICHD Neonatal Research Network participating in the trial are listed below. The NICHD center number is indicated in parentheses next to the name of each center. The Neonatal Research Network principal investigators (PIs) are located in the second column, the Follow-up PIs in the third column and the SUPPORT Study PIs in the fourth column.

PARTICIPATING CENTERS	NRN PI	NRN Follow Up PI	SUPPORT STUDY PI
Case Western Reserve Univ. (3) Rainbow Babies and Children's Hospital	Michele Walsh, MD	Dee Wilson, MD	Michele Walsh, MD
University of Texas-Dallas (4)	Charles Rosenfeld, MD	Roy Heyne, MD	Walid Salhab, MD
Wayne State University (5) Children's Hospital of Michigan	Seetha Shankaran, MD	Yvette Johnson, MD	Seetha Shankaran, MD
University of Miami (8) Jackson Memorial Hospital	Shahnaz Duara, MD	Charles Bauer, MD	Shahnaz Duara, MD
Emory University (9) Grady Memorial Hospital	Barbara J. Stoll, MD	Ira Adams-Chapman, MD	Susie Buchter, MD
University of Cincinnati (11) University of Cincinnati Hospital	Edward F. Donovan, MD	Jean Steichen, MD	Vivek Narendran, MD Kurt Schibler, MD
Indiana University (12)	James A. Lemons, MD	Anna M. Dusick, MD	Brenda Poindexter, MD
Yale University (13) The Children's Hospital at Yale – New Haven	Richard A. Ehrenkranz, MD	Linda Mayes, MD	Vineet Bhandari, MD
Brown University (14) Women and Infant's Hospital	William Oh, MD	Betty R. Vohr, MD	Abbot Laptook, MD
Stanford University (15) Stanford University Med Center	David K. Stevenson, MD	Susan R. Hintz, MD	Krisa Van Meurs, MD
University of Alabama (16) University of Alabama at Birmingham	Waldemar A. Carlo, MD	Myriam Peralta, MD	Waldemar A. Carlo, MD
University of Texas- Houston (18)	Jon E. Tyson, MD	Jon Tyson, MD	Brenda Morris, MD
Duke University (19)	Ronald Goldberg, MD	Ricki Goldstein, MD	C. Michael Cotten, MD
Wake Forest University (20)	Michael O'Shea, MD	Robert Dillard, MD	Michael O'Shea, MD
Golisano Children's Hospital at Strong (21) University of Rochester	Dale L. Phelps, MD	Gary Myers, MD	Nirupama Laroia, MD
University of California-San Diego (22)	Neil Finer, MD	Yvonne Vaucher, MD	Neil Finer, MD

2.3 Responsibilities of Clinical Centers

The minimum staff required for network participation at each clinical center is the physician Principal Investigator (PI), the Research Coordinator, and telephone interviewers, if interviews are not conducted by the Research Coordinator.

The research coordinator may identify another individual to conduct the telephone interviews. In this situation, it will be the coordinator's responsibility to assure that the interviewer is certified in standardized administration of the questionnaire (see below). The responsibilities of these individuals are described briefly in this chapter and in more detail in subsequent chapters.

The PI or designee is responsible for ensuring the proper conduct of the trial at his or her clinical center (including recruitment and treatment of patients as specified in the protocol), accurate collection of data and transmission of information to the Data Coordinating Center (DCC). Other specific duties include the following:

- Presenting an in-service to the other physicians
- Applying for IRB approval
- Introducing the study to the parents of prospective patients, and obtaining signed informed consent from the parents of eligible infants (in some centers this responsibility may be delegated)
- Reviewing all infants for whom informed consent has been obtained to confirm their eligibility
- Informing the IRB of the study progress.

The Research Coordinator will be responsible for the day-to-day operations of the study at the clinical center, including data collection and management. This responsibility includes the following:

- Collecting information necessary to complete the data collection forms, and coordinating data entry
- Training and certifying the staff in the use of the network computer
- Controlling access to the network computer and ensuring that required back-up, security and confidentiality are maintained
- Responding to edit messages and other communications from the data center
- Distributing updates of the protocol and of the manual of operations to clinical center staff
- Further responsibilities are based on the study administration option chosen by the center.

2.3.1 Delineation of Responsibilities by Study Administration Option

Clinical Centers have the option of administering the follow-up questionnaires to their own patients (Option 1) or having telephone interviewers of the University of Rochester Health Services Research Group administer the follow-up questionnaires to their patients (Option 2). Table 2 indicates which option the centers have chosen.

Table 2. **SUPPORT Trial - Pulmonary Outcomes Study**

NICHD Site	*6, 12 and 18-22 Month Pulmonary Questionnaires Administered By*	Option Number
Alabama	Alabama	1
Brown	Brown	1
Cincinnati	Cincinnati	1
CWRU	CWRU	1
Dallas	Dallas	1
Duke	Duke	1
Emory	Rochester	2
Houston	Rochester	2
Indiana	Rochester	2
Miami	Miami	1
Rochester	Rochester	2
Stanford	Rochester	2
UCSD	UCSD	1
Wake Forest	Wake Forest	1
Wayne State	Wayne State	1
Yale	Yale	1

Regardless of the option chosen, each local center is responsible for obtaining informed consent, administering the NICU Discharge-Baseline Interview (SUPF01) and distributing the respiratory diary to parents, as well as tracking patients following discharge. Table 3 further describes the responsibilities of the local center and Rochester in Option 1 and Option 2.

Table 3.	Option 1	Option 2	
	Local Center	Local Center	Rochester
Consent / IRB	✓	✓	
Questionnaire at Discharge	✓	✓	
Patient Tracking	✓	✓	
Questionnaire at 6 & 12 mo.	✓		✓
Questionnaire at 18-22 mo.	✓		✓
Data Entry (questionnaires)	✓		✓

Each of the responsibilities discussed in table 3 above will be discussed separately below.

2.3.2 Consent

For both options, every effort will be taken to enroll ALL SUPPORT patients into the Pulmonary Outcomes Study, including both currently enrolled SUPPORT patients (both patients still in NICU and those discharged from the NICU) and all future enrollees. By obtaining pulmonary outcome data for both current and future SUPPORT patients, death or adverse pulmonary outcome can be analyzed as competing outcomes. Sample consent forms for currently enrolled and future SUPPORT patients are attached.

2.3.3 Discharge Questionnaire

The purpose of the discharge questionnaire is to assure adequate randomization of important covariates affecting outpatient respiratory health and to obtain baseline data on home environment and family history of respiratory diseases. There are a total of 16 questions on the questionnaire; 9 questions on home environment and exposures, 1 question on alternate contact information, 6 questions on family history of allergy and respiratory problems.

Each center, regardless of study option chosen, will administer the discharge questionnaire. This will allow ascertainment of baseline data as well as confirming contact information for the family. For patients enrolled into the Pulmonary Outcomes Follow up Study after NICU discharge, this questionnaire can be administered prior to the 6 month questionnaire.

After completing the discharge questionnaire, parents should be given the respiratory diary and instructed to record how often their baby has wheezing or coughing, whether the baby visited a doctor's office, emergency room or was hospitalized for breathing problems. Parents should be asked to gather the diary and any medications or other information about their baby's breathing when the interviewer calls in six months.

2.3.4 Tracking

All centers (Option 1 and 2 centers) will track their own patient's telephone and contact information for the purpose of administering telephone questionnaires at 6, 12 and 18-22 months. This will also help assure attendance at the routine NICHD neurodevelopmental follow up clinic visit 18-22 months.

The following core set of contact information is recommended for all enrolled patients.

- Network number
- Patient Name
- DOB
- Gender
- Name of Prior Interview Respondent (if different than primary care taker)
    - Primary Caretaker Contact Information
        - Name
        - Relationship to patient
        - Mailing address
        - Telephone number #1
        - Telephone number #2
    - Secondary (Backup) Caretaker Information
        - Name
        - Relationship to patient
        - Mailing address
        - Telephone number #1
        - Telephone number #2

2.3.5 Responsibility of Option 1 Centers In Administering Questionnaires at 6, 12 And 18 Months' Corrected Age

Clinical Centers will have the option of administering the follow-up questionnaires to their own patients (Option 1) or having telephone interviewers from the University of Rochester Health Services Research Group administer the follow-up questionnaires to their patients (Option 2).

- Standardization of Interview Technique
  - In order to assure that interviews are administered in a standard and consistent manner, the University of Rochester Health Services Research Group will conduct an Interviewer Certification Program to train interviewers at Option 1 centers and Rochester based interviewers. All interviews must be performed by certified interviewers (see 2.4.7 below).

- Conducting the Interviews
  - Prior to each interview, a postcard will be mailed to the family reminding them to expect a telephone call.
  - For centers that see patients in an office setting, the questionnaire may be administered face to face.

2.3.6 Responsibility of Option 2 Centers In Administering Questionnaires at 6, 12 And 18 Months' Corrected Age

- Upon receipt of RTI reminder, Option 2 Centers will send a postcard to the family reminding them to expect a telephone call.
- Review and update contact information as necessary and fax contact information to the Rochester Health Services Research Group (RHSRG).
- The RHSRG will conduct the telephone interview.
- At the conclusion of each interview, contact information will be confirmed and updated contact information faxed back to the Option 2 Center.

2.3.7 Responsibilities of the University of Rochester Health Services Research Group

- The certification program will consist of two parts.
  - Part 1 - a teleconference training session during which each question on the questionnaires is reviewed and discussed with the interviewers. The goal is to assure that interviewers understand the purpose of each question and, in a standard way, how to deliver the question, elicit an answer and record the interviewee's response.

  - Part 2 will consist of a practice interview in which interviewers from each center interview the Rochester trainer, who simulates a standardized patient. Following the practice interview, the Rochester trainer and practice interviewer will discuss the interview and give feedback.

- Other responsibilities include:

- Development and distribution of an audio clip of wheezing to be presented along with a verbal definition to the interview respondent to standardize interpretation of wheezing and to minimize ascertainment biases due to language, culture, literacy or interviewing techniques.

- Maintaining trained Spanish-speaking individuals to conduct the telephone interviews with Spanish-speaking participants from centers choosing Rochester to administer the questionnaire to their patients (Option 2).

- Spanish language versions of the questionnaires will be created and made available to all centers. The Cornell Translation Service, a University based professional translation service, will be contracted by the University of Rochester to perform the translation.

2.4 Responsibilities of the Data Coordinating Center

The DCC at RTI International is responsible for all aspects of statistical design and analysis as well as data management of the study. In particular, this includes:

- Processing, updating and distributing the protocol and manual of operations
- Developing and distributing the data forms, including periodic updates as necessary
- Developing, testing and implementing the database and other software. Ensuring that data are correct and complete by implementing editing and auditing procedures
- Monitoring the progress and quality of the study
- Preparing interim and final analyses and reports
- Participating in the preparation of presentations and publications relating to the study

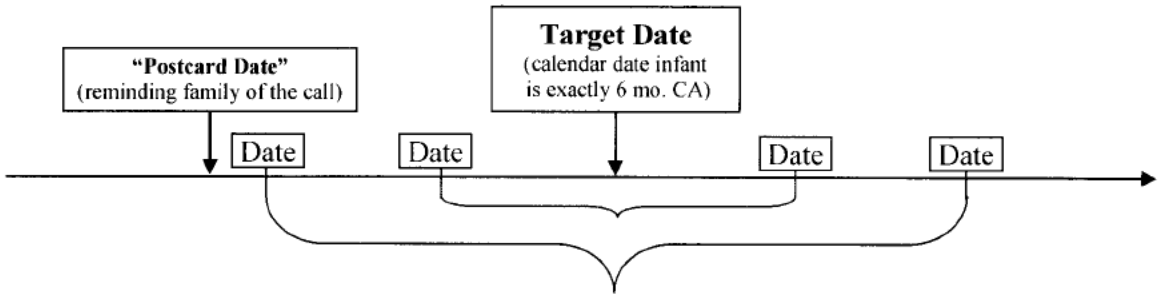
The DCC is also responsible for sending monthly reminder reports to Network Centers. For patients enrolled in the Pulmonary Outcomes Study, the DCC will send a monthly reminder to each center with a list of IDs that are due to have questionnaires conducted. The report will include the following:

- Network number
- Gestational age
- Gender
- Date of last interview
- Care taker (relationship code) providing the previous interview
- Whether the previous interviews were conducted face to face or by telephone
- List of the 4 interviews that have been completed (CA = corrected age)
- Completed interview dates, dates of previous interviews and interviewee information may be presented as outlined in the table below.

Example table

Required Interviews	Date	Caretaker Interviewed	Face to Face?
▪ Discharge	__/__/__	_____	Y or N
▪ 6 month CA	__/__/__	_____	Y or N
▪ 12 month CA	__/__/__	_____	Y or N
▪ 18-22 month CA	__/__/__	_____	Y or N

- Target date for the current interview with windows within which interview should be accomplished, goal window (target date ± 2 weeks) and acceptable window (target date ± 4 weeks)
- A "postcard date", 5 weeks prior to the contact, when a postcard might be sent to the family reminding them of the upcoming call or visit



2.5 Responsibilities of NICHD

In addition to its role as a funding agency, the NICHD participates in the activities of the cooperative agreement by being represented on the Steering Committee. The Program Official also participates in the development of protocol and in assisting the Steering Committee in the coordination of the studies conducted by the Network. The NICHD Program Official, in conjunction with the RTI Principal Investigator is responsible for monitoring site performance of all participating centers. The Program Official has the following responsibilities:

- Assistance in the development of the study protocol.
- Assistance in the development of capitation-based budgets, including the identification of study costs and special institutional needs.
- Allocation of network resources to meet study needs.
- Facilitation of training meetings, site visits, and subcommittee meetings.
- Participating in preparation of publications.

Chapter 3
Screening, Eligibility, Consent

3.1 Study Population

This follow-up study will include all surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial, which were inborn infants of 24 0/7ths to 27 6/7th weeks at birth for which a decision was made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) were enrolled.

Inclusion Criteria

- Enrollment in the SUPPORT Trial
- Survival to hospital discharge
- Consent for enrollment into the Pulmonary Outcomes Follow up Study, obtained either at the time of enrollment into the SUPPORT Trial or separately.

3.2 Exclusion Criteria

- Refusal of informed consent

3.3 Informed Consent

Every effort will be taken to enroll ALL SUPPORT Trial patients into the Follow-up Study, including currently enrolled SUPPORT patients (both patients still in NICU and those discharged) and future enrollees. By obtaining pulmonary outcome data for both current and future SUPPORT patients, death or adverse pulmonary outcome can be analyzed as competing outcomes. Each local center will be responsible for obtaining informed consent for the Follow-up Study regardless of whether they are administering the follow-up questionnaires to their patients or Rochester is conducting the telephone interviews.

For future enrollees in the SUPPORT Trial, consent for the Follow-up study will be obtained at the time of enrollment in the main trial. As described in the SUPPORT Trial Manual of Operations, these infants will be recruited for the study by approaching one or both parents at the time of admission to the hospital at risk for premature delivery at 27 weeks or less. It is anticipated that, whenever possible, the parents will be approached by study personnel to discuss the trial and obtain an informed consent for the participation of the infant at delivery. Randomization will be by family, thus all offspring will be randomized to the same trial arms, provided adequate equipment and personnel are available at the time of delivery. Sample consent forms for currently enrolled and future SUPPORT patients are attached (Appendix C).

3.4 Screening Procedures

This follow-up study will include all surviving infants enrolled, randomized and treated as part of the NICHD Neonatal Research Network SUPPORT Trial.

For future enrollees in the SUPPORT Trial, all admissions for threatened premature delivery will be screened on a daily basis to ensure that eligible patients can be enrolled. Obstetrical colleagues at each participating institution will be informed of the nature of this study and encouraged to discuss this study with their patients at risk of premature delivery. The study coordinator at each site will maintain a screening log of potentially eligible patients. In addition, the usual practice of neonatal consultation for all such at risk deliveries will provide a second opportunity to approach mothers with fetuses at risk of preterm delivery.

Chapter 4
Randomization

4.1 Randomization Procedures

Randomization for the NICHD Neonatal Research Network SUPPORT Trial was stratified by gestational age group (24 - 25 6/7 and 26 - 27 6/7) and occurred prior to delivery for consented deliveries. The randomizations were performed by utilizing specially prepared envelopes. The Data Center prepared brown sealed envelopes which contained the identity of the treatment combination that were assigned to the infants enrolled into the study. Deliveries were randomized as a unit, thus multiples, twins, triplets etc were randomized to the same arm of the trial. One envelope corresponded to the delivery of a consenting mother regardless of the number of babies delivered so that all babies from a given delivery received the same treatment combination.

Refer to Section 4.1.1 of the NICHD Neonatal Research Network SUPPORT Trial Manual of Operations (MOO) for more information on randomization and masking as well as storing and assigning oximeters that occurred during the main study.

During the Follow-up Study activities, research coordinators and telephone interviewers, if different from the research coordinators, will remain blinded as to whether infants were randomized to the control or treatment group.

Chapter 5
Follow-up Study Procedures

5.1 SUPPORT Trial Study Interventions

Refer to Chapter 5 of SUPPORT Trial Manual of Operations (MOO) for more information on the study interventions and the procedures for the treatment groups. The same questionnaires will be administered to both treatment groups in the Follow-up Study.

5.2 Pulmonary Follow Up Study Interventions

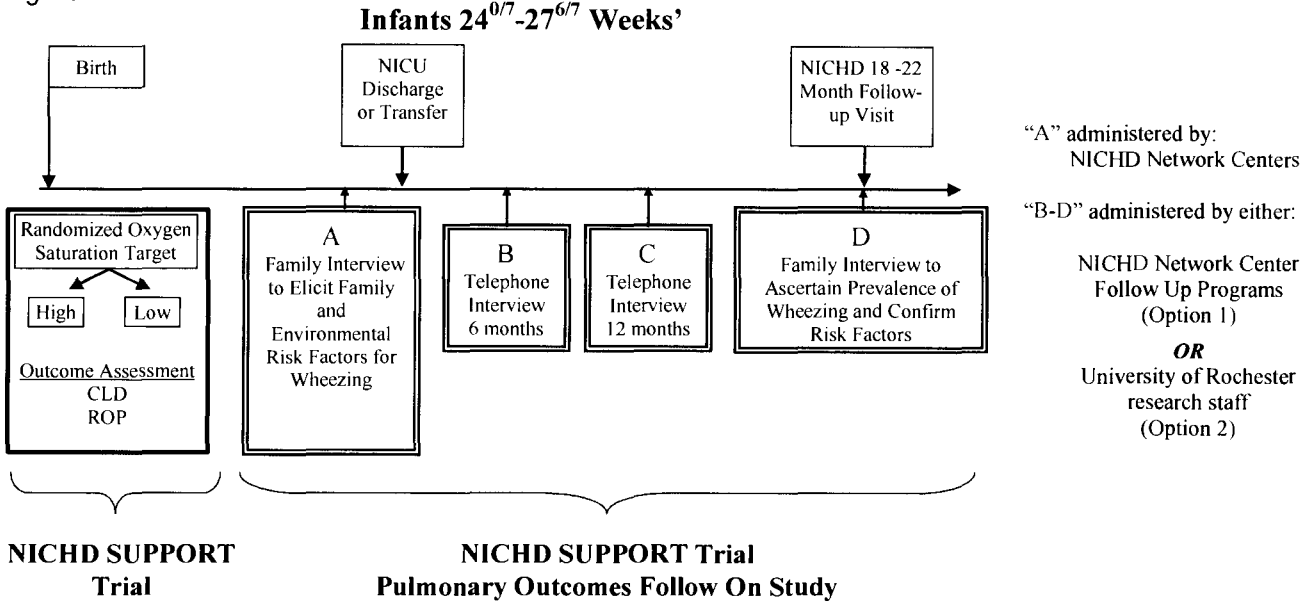
Before delivery, infants will be randomized according to the 2x2 factorial design of the SUPPORT Protocol.

The SUPPORT Follow-up Study of Pulmonary Outcomes begins just prior to NICU discharge. See Figure 1 for a diagram of the SUPPORT Trial Follow-up Study procedures.

Four questionnaires will be administered at approximately 6 month intervals until the baby is 18-22 months' corrected age according the schedule outlined in Figure 1. Each interview will collect a 6 month interval history, which, when taken together, will provide a complete respiratory history over the first 18-22 months' corrected age. If a questionnaire is not completed, the subsequent questionnaire will include the full interval history since the last completed questionnaire.

SUPPORT Trial Follow-up Study

Figure 1.



DESCRITION OF QUESTIONNAIRES

A) Discharge Questionnaire Administered by Network Centers

The discharge interview consists of a primary caretaker (parent or guardian) interview to elicit family and environmental risk factors for wheezing and cough. The family interview will be administered at each participating Network Center by site study nurses prior to NICU discharge or transfer. The questions are based on intake questions used by the Tucson Respiratory Study and are designed to elicit family history of asthma, atopy, and home environmental exposures and to identify likely care givers.

The purpose of the discharge questionnaire is to assure adequate randomization of important covariates affecting outpatient respiratory health and to obtain baseline data on home environment and family history of respiratory diseases. There are a total of 16 questions on the questionnaire; 9 questions on home environment and exposures, 1 question on alternate contact information, 6 questions on family history of allergy and respiratory problems.

Each center, regardless of study option chosen, will administer the discharge questionnaire and perform data entry. This will allow ascertainment of baseline data as well as confirming contact information for the family.

B) Respiratory History Questionnaires Administered at 6 and 12 Months' Corrected Age

The purpose of this questionnaire is to obtain an **interval** respiratory history. Questions are designed to collect respiratory history in areas outlined in the table at right. For centers choosing Option 1, interviews may be conducted either by telephone or face to face. For centers choosing Option 2, interviews will be conducted long distance by telephone from The Rochester Health Services Research Group to the family.

Outcome	Question No.
Respiratory Symptoms	9, 10, 13-15
Quality of Life	11, 12
Health Services Utilization	
Office	6
Emergency Department	7
Hospitalization	8
Medication Use	27
Oxygen Use	26
Preventive Services	24, 25
Exposures	16-23

C) Respiratory and Environmental Exposure History Questionnaires Administered at 18-22 Months' Corrected Age

The purpose of this questionnaire is to obtain an **interval** respiratory history and to identify environmental exposures that may increase the likelihood of symptomatic airway dysfunction. Questions are designed to ascertain the frequency and severity of wheezing and cough episodes and to assess the need for outpatient pulmonary care. In addition, a history of atopy is elicited. There are a total of 30 questions, encompassing questions from the discharge and 6 and 12 month questionnaires.

This parent interview may also be administered either by telephone prior to the regularly scheduled 18-22 month NICHD developmental follow-up clinic visit or face to face at the

time of the visit. Contacting parents prior to the office visit will help improve the Developmental Follow Up Clinic attendance rate. Otherwise, the clinic visit will provide a back up means to contact the family. The 18-22 month interview will be conducted either by the local NICHD Follow Up Program (Option 1) or long distance from Rochester (Option 2), based on center preference (see table 2 below).

5.3 Administration of the Follow-up Questionnaires

- The questionnaires are for research only. Caretakers, parents or guardians expressing concern regarding the child's breathing should be encouraged to discuss their concern with the family's primary care physician. Diagnostic or treatment advice should NOT be offered as part of the interview.

5.4 Protocol Violations

The occurrence of any one of the following criteria will determine whether an individual infant will be considered a protocol violation:

- Interview occurring outside the window
- Missed interview

In both of these cases the interview should be conducted at the next available opportunity and should encompass respiratory health since the prior interview.

All protocol violations will be reviewed by the center PI who will discuss each protocol violation with the involved clinicians, identifying steps to avoid future violations.

5.5 Adverse Events

We anticipate no risk to the patient from this observational follow-up study.

Serious adverse events were anticipated in the main SUPPORT Trial for this vulnerable population. Refer to Section 5.5 of the NICHD Neonatal Research Network SUPPORT Trial MOO for more information on adverse event reporting and monitoring.

Chapter 6
NICU Discharge-Baseline Interview

Introduction

The purpose of the discharge questionnaire is to assure adequate randomization of important covariates affecting outpatient respiratory health and to obtain baseline data on home environment and family history of respiratory diseases. There are a total of 16 questions on the questionnaire; 9 questions on home environment and exposures, 1 question on alternate contact information, 6 questions on family history of allergy and respiratory problems.

Each center, regardless of study option chosen, will administer the discharge questionnaire and perform data entry. This will allow ascertainment of baseline data as well as confirming contact information for the family.

Instructions for Completing the NICU Discharge-Baseline Interview (SUPF01)

Timing of the Interview:

This interview should be administered to the parent/guardian by a trained study nurse prior to or within the first 30 days following NICU discharge. If for any reason the infant is enrolled into the Pulmonary Outcome Study later than 30 days following NICU discharge, the questionnaire should be administered prior to interval questionnaires (SUPF02 or SUPF03)

Heading- Infant's Identification
The following information is included in the heading section of all patient specific data forms: Center, Site, Network Number, SUPPORT Follow-up Number, Birth Number and Mother's Initials **(optional).** This information should be completed on the first page of the interview and the SUPPORT Follow-up Number written on subsequent pages in case the completed form pages are separated.

6.1 Conducting the Interview

6.1.1 Initiating the interview:

Script Introducing the Study:
N.B. The interviewer's script is in italics and enclosed in quotations.

"Premature babies are more likely than full term babies to have breathing problems after discharge from the NICU. The purpose of this study is to see whether or not the treatments your baby received as part of the SUPPORT Study improves your baby's breathing in the 18-22 months following the baby's due date.

As part of this study, we will contact you every 6 months or so to ask you questions about your baby's breathing. The questions will be about your baby's breathing symptoms, especially wheezing and coughing, and about your baby's need for medical visits and treatments for breathing problems.

By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical.

We have prepared a diary for you to help you keep track of your baby's breathing, especially breathing problems and treatments.

Give diary

To complete the diary, please record how often your baby has wheezing or coughing, whether your baby visited a doctor's office, emergency room or was hospitalized for breathing problems.

When we call, we'd like you to gather the diary and any medications or other information about your baby's breathing.

In order to help us understand your baby's breathing and risk for breathing problems at home, we'd like to ask you a few questions about your home and about whether breathing problems run in the family. As with all information we collect, the answers to these questions will be kept confidential."

Please confirm the study baby's identity.

"We will be discussing, patient name. He/she is a boy/girl born on birth date"
Question 1.
Child's Name:
Please enter the child's name including, nickname that he/she will be called.

Question 2.
Enter the date of the interview in "mm/dd/yyyy" format.

Question 3.
Child's Sex:
Please enter the child's sex.

Question 4.
Child's Birthdate:
Please enter to the child's birth date in "mm/dd/yyyy" format.

Please confirm the identity of the caretaker being interviewed.
Question 5.
"With whom am I speaking?
Question 5a.
What is your relationship to the baby?"

Please specify the primary caretaker's name and relationship to the infant using the relationship codes used in the Network Follow up Program, Appendix B.

Every effort should be made to interview the primary caretaker during this interview and all subsequent interviews (6, 12 and 18 months). If the mother resides in the same household as the child, the mother is the primary caretaker. If each caretaker has exactly 50% custody,

record as the primary caretaker, the person who comes in for the discharge. This person should answer all subsequent interviews, if possible.

APPENDIX B

RELATIONSHIP CODES

The following codes are used to identify the primary caretaker.

001 - Mother of Child
002 - Father of Child
011 - Husband, Significant Other (SO)(if different from 002)
012 - Wife, Girlfriend (if different from 001)
021 - Maternal grandmother
022 - Paternal (SO) grandmother
031 - Maternal grandfather
032 - Paternal (SO) grandfather
041 - Maternal aunt
042 - Paternal (SO) aunt
051 - Maternal uncle
052 - Paternal (SO) uncle
061 - Brother
062 - Step Brother
071 - Sister
072 - Step Sister
081 - Maternal female cousin
082 - Paternal (SO) female cousin
091 - Maternal male cousin
092 - Paternal (SO) male cousin
101 - Other maternal relative
102 - Other paternal (SO) relative
201 - Foster mother
202 - Foster father
301 - Adoptive mother
302 - Adoptive father
401 - Other non-relative
402 - Social worker/case worker
501 - Staff in congregate care
502 - Still hospitalized
504 - Unknown

Question 6.
Type of Interview:
Record whether the interview conducted face to face or by telephone.

Interview Begins
(N.B. The interviewer's script is in italics and enclosed in quotations)

Script: ***"At this time, we would like a little information about the environment in which your new child will grow up."***

Question 7.

"First, how many people normally live with you in your home for at least 6 months of the year?"

Enter the total number of household members. A household member is a person who spends more than 7 nights in the home over a two week period for at least 6 months of the year.

Question 8.

"After the first few months, will your child be sharing a room with other family members on a regular basis?"

Enter YES if child shares a room with another household member more than 7 nights in a 2 week period.

Question 8a.

If answer to 8 is YES: *"How many people will sleep in the same room with him/her?"* Please record how many people will sleep in the same room with the child.

Question 9.

"*How many rooms are there in your house, excluding closets and bathrooms?"* Record how many rooms in the space provided.

A room is a space within the house in which residents play, sleep, work or eat.

Question 10.

"Do you have any pets inside the home?"

If yes record, *"How many dogs in the home? Cats in the home? Do you have other pets in the home? What kinds? How many?"*

If interviewee reports pets, please record the number of dogs and cats separately. Group all other pets together and record total number of pets that are neither a dog nor a cat.

Question 11.

"Does your home or apartment have air conditioning or some kind of cooling?"

Please enter "Yes" or "No"

Question 11.a-11.c Please record whether family has air conditioning or evaporative cooling. If family uses another type of home cooling system, please answer YES and record type.

Question 12.

"How is your home heated?, With steam or hot water, with a gas furnace, with electricity, with a wood stove, or something else? "

Please prompt by reading each of the listed heating options. Record all heating methods used in the home or apartment. If more than one heating type is used, please record all heating types used. Steam or hot water heat uses upright radiators or baseboard units. A central gas furnace uses forced air vents that blow air into the room. Included in wood stove heat is use of a fireplace for heat, including fireplaces with energy conserving "inserts".

Question 13.

"What fuel is used most for cooking in your home?"

There is no need to prompt with each alternative cooking fuel. Please record one primary cooking method used in the home or apartment.

Scripting: "The next questions are about your baby's diet ....."

Question 14.
"Is your child receiving only breast milk, only formula, or both breast milk and formula?"
Record response

Question 14a.
If reply to 14 is only breast milk (choice #1),
"*Will the breast milk be supplemented with formula in the next 6 months?"*
Please record "Yes", "No" or "Don't Know

Question 14b.
"If so, when do you think the supplement will begin?"
Enter YES, if breast milk will be supplemented with formula. Enter the number of months from date of interview that breast milk will be supplemented with formula.

Scripting: "The next question are about your baby's care environment ....."

Question 15.
"Does the mother plan to work outside the home within the next year?"
Select from responses below.
1. Yes
2. No
3. Don't Know

Scripting: "The next questions are about smoke exposure....."

Question 16.
"Which one of the following 3 statements best describes the situation regarding smoking in your child's ***home?****.....Read all options to the interviewee before recording a response: Smoking is allowed in any common room of the home, smoking is limited to part of the house where the child rarely goes, there is no smoking inside at all?*

Question 16a.
If answer to question 16 is "there is no smoking in the house at all", then ask question 13a, *"Are there any exceptions to this situation?"*
If respondent reports any exceptions, record "Yes". If no, skip to question 17.

Question 16b.
If answer to 16a is "Yes", then ask question16b.
"Under what circumstances are the exceptions allowed?"
Record a brief response as free text.

Question 17.

"*Which one of the following 5 statements best describes the situation regarding smoking in your* ***car?****…. Read all options to the interviewee before recording a response: Smoking is usually or always allowed, smoking is sometimes allowed, smoking occurs in the car only when the child is not inside, there is no smoking inside the car*"

Record the response as it applies to the main automobile in which the baby rides. If family does not ride in a car (public transportation only or baby doesn't leave home), record response #1.

Questions 17a and 17b. Responses questions to17a and 17b are completed similarly to questions 16a and 16b.

Question 18.

"How often have you smoked since this child was born?"

Please record response, never means never, daily means at least once per day, record occasionally for any quantity between never and daily.

Question 19.

"Altogether, how many people in the child's home smoke?" _____people

Record the number of people who reside in the home (spend more than 7 out of 14 nights in the home) who smoke. Any smoker counts, whether they smoke in the home, outside the home or at some distant location.

Family History Form

Scripting: "In the next section, we'd like to know what breathing and allergy problems run in the family."

Administer the attached Family History Questionnaire using the follow script.

Mother:

"We'll start with the baby's mother. How old is the baby's biologic mother? Does she have bronchitis, emphysema, COPD, bronchiectasis, asthma, inhaled allergies, or food allergies?"

"Does she (you) have any other chronic respiratory illnesses?"

"How often do you smoke in the baby's home?"

Father:

"For the baby's biologic father, is he living? How old is he? Does he have bronchitis, emphysema, COPD, bronchiectasis, asthma, inhaled allergies, or food allergies?"

"Does he have any other chronic respiratory illnesses?"

"How often does he smoke in the baby's home?"

Complete the remainder of the table by collecting the same medical history using the script above.

Please complete a family history for each of the family relationships listed, mother, father, maternal grandmother (Mom's biologic Mother), maternal grandfather (Mom's biologic Father), paternal grandmother (Dad's biologic Mom), and paternal grandfather (Dad's biologic Father). For each relative above, enter whether they have ever had any of the listed respiratory problems. The interviewer need not explain each diagnosis, but may offer an explanation if asked. Record only those responses that pertain to the baby's biologic relatives.

Question 20.

"Finally, which friend or relative is most likely to be able to contact you 6 months from now in case we lose contact with you?"

Record the information for an alternate contact person who is unlikely to move and the most likely to know the baby's family most recent residence / phone number.

Chapter 7
6 and 12 Month Pulmonary Outcome Questionnaires

Introduction

The purpose of this questionnaire is to obtain an **interval** respiratory history, such that when the 6, 12 and 18-22 month questionnaires are taken together, a complete respiratory history over the time period is collected.

The questionnaire will be administered to the parent or guardian by a certified telephone interviewer at 6 months' CA and again at 12 months' CA.

Centers choosing Option 1 will administer the questionnaire using a certified local interviewer and locally maintained contact information. For centers choosing Option 2, a Rochester Health Services Research Group (RHSRG) certified interviewer will conduct the interview via long distance telephone call using contact information maintained by the local center and faxed or emailed to the RHSRG.

Instructions for Completing the 6 and 12 Month Questionnaire (SUPF02)

Instructions for Completing the NICU Discharge-Baseline Interview (SUPF01)

Timing of the Interview:

This interview should be administered by a certified study interviewer. The target window for this interview is at the following corrected ages: 6 months ± 2 weeks and 12 months ± 2 weeks, with an acceptable window of 6 months ± 1 month and 12 months ± 1 month. If for any reason the infant is enrolled into the Pulmonary Outcome Study later than this time window or becomes available for a Pulmonary Outcomes Interview outside this window, the questionnaire should be administered, collecting an interval history from the time of NICU discharge or the most recent interview, whichever is most recent.

Heading- Infant's Identification
The following information is included in the heading section of all patient specific data forms: Center, Site, Network Number, SUPPORT Follow-up Number, Birth Number and Mother's Initials **(optional).** This information should be completed on the first page of the interview and the SUPPORT Follow-up Number written on subsequent pages in case the completed form pages are separated.

7.1 Conducting the Interview

7.1.1 Initiating the interview:

Please request and confirm the identity of the caretaker who completed the initial interview.

Every effort should be made to interview the primary caretaker who completed the initial interview (hereafter referred to as the primary respondent) during this interview and all subsequent interviews (6, 12 and 18 months). If the mother resides in the same household as the child, the mother is the primary caretaker. If each caretaker has exactly 50% custody,

record as the primary caretaker, the person who comes in for the discharge. This person should answer all interviews, if possible.

The interviewer will need to ask for the primary respondent. In the event that the primary respondent is not available, arrangements should be made to call back at a time when the primary respondent will be free to complete the interview. At least 3 call attempts should be made to reach the primary respondent, after that a secondary respondent, who is familiar with the baby and his or her respiratory health, can be identified to complete the interview.

Introduction Script:
When parent or primary care giver is on phone:

"Hello, my name is <your name>. I am calling from the <NICHD Center>. As you probably remember, when you were in the NICU you enrolled in our study about respiratory health of premature infants. I am calling to ask you some questions about your baby's breathing. It will take about 10-20 minutes to complete. Is this a good time for you?"

"Before we begin this interview, it would be helpful if you could gather the breathing diary given to you when you left the NICU as well as any medications your child has been prescribed or has been taking and have them in front of you. As with all information we collect, the answers to these questions will be kept confidential."

Question 1.
Please enter date of the interview.

Please confirm the identity and contact information for the study baby to be interviewed.

"We will be discussing, patient name. He/she is a boy/girl born on birth date"
Child's Name:
Please enter the child's name.

Child's Birthdate:
Enter to the child's birth date in "mm/dd/yyyy" format.

Child's Telephone Number:
Enter the telephone number to the child's home.

Child's Address:
Enter the address of the child's home.

Alternate Contact Information
Which friend or relative is most likely to be able to contact you 6 months from now in case we lose contact with you?"

Confirm the contact information for an alternate contact person who is unlikely to move and the most likely to know the baby's family most recent residence / phone number.

Question 2a. and 2b.
Enter name and relationship code of the person being interviewed.

Please specify the primary caretaker's name and relationship to the infant using the relationship codes used in the Network Follow up Program.

Question 3.
Type of interview.

Please specify and record whether the interview was administered face to face or via telephone.

Question 4.
Location of Interview.

Please specify and record whether the interview was administered at the local center (Option 1) or by the Rochester site (Option 2).

Instructions:
Parents or guardians expressing concerns regarding their child's breathing should be advised to discuss them with the family's primary care physician.

Where the phrase "last contact" is used below, please substitute with the most specific relevant time prompt, e.g. for the 6 month interview, refer to "since NICU discharge"; for the 12 month interview, refer to "over the past 6 months", etc.

Interview begins:
(N.B. The interviewer's script is in italics and enclosed in quotations)

Scripting:
"Some of these questions will be familiar to you. Since we last spoke (__ __) months ago on (__ __/__ __/__ __) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing problems your child may have....."

Question 5.
"Has the child been with you during the past 6 months?"

Please enter "Yes" or "No". If child has been with the interviewee less than 6 months, please enter "No".

Scripting: "Since <our last contact> with you about your child....."

Please replace the phrase "our last contact", with an interview specific prompt, e.g. "since discharge from the NICU" at the 6 month interview or "since our telephone conversation 6 months ago", for the 12 and 18 month interviews. Equivalent phrases may be used.

Question 6.
"How many times has your child visited a doctor's office?" |___|___| times

Record the number of times that the baby visited the doctor's office for any reason.

Question 6a.
"How many of these times were because of wheezing or breathing problems?"

Record the number of times that the baby visited the doctor's office with breathing problems as one of the 2 major concerns for the visit.

Scripting: "Since <our last contact> with you about your child....."

Please replace the phrase "our last contact", with an interview specific prompt, e.g. "since discharge from the NICU" at the 6 month interview or "since our telephone conversation 6 months ago", for the 12 and 18 month interviews. Equivalent phrases may be used.

Question 7.

"How many times has your child visited an Emergency Department (Emergency room)?"

|___|___| times

Record the number of times that the baby visited the emergency department or emergency room for any reason.

Question 7a.

"*How many of these times were because of wheezing or breathing problems?*"

Record the number of times that the baby visited emergency services with breathing problems as one of the 2 major concerns for the visit.

Question 8.

"How many times has your child stayed in the hospital for 1 or more nights in a row?"

|___|___| times

Record the number of times the baby was hospitalized for any reason, i.e the number of hospitalizations, not the number of hospitalized days.

Question 8a.

"How many of these times were because of wheezing or breathing problems?" |___|___| times

Record the number of times that the baby was hospitalized with breathing problems as one of the 2 major concerns for the visit.

Script:

"The next questions are about your baby's breathing. .....

The first question is about wheezing. By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical."

Question 9.

"Since <our last contact> with you, has your baby's chest sounded wheezy or whistling?"

Enter yes if the respondent reports that the baby's chest has sounded wheezy or whistling. The interviewer may repeat the verbal and audio descriptions of wheezing may be repeated to the respondent. If respondent answers "I don't know", interviewer should ask respondent to think back over the time period, repeating the description. If parent is still not sure, record "don't know".

Question 9a.

"Has your baby's breathing sounded like this?" ***(play audio clip of wheezing).***

This question is intended for all respondents, regardless of whether they reported wheezing in question 9. The audio clip is from a patient with severe, audible wheezing and represents only one of many manifestation of wheezing breathing sounds. If asked, the interviewer may say that this represents just one type of wheezing. We wish to know about all wheezing and therefore we asked two questions.

Record response, "Yes" or "No". If respondent replies "no" or "don't know", interview skips to question 10. If yes, proceed to questions 9b-g.

Question 9b.

"Has this occurred with colds?"

A "cold" is an upper respiratory infection; other phrases for a "cold" include, "head cold", "rhinitis, "runny or water nose" or "sniffles". A cold may be complicated by an otitis media (ear infection).

A "cold" does not include "chest cold", "bronchitis", "pneumonia", or "bronchiolitis".

Question 9c.

"Has your child's chest sounded wheezy or whistling apart from colds?"

Enter "yes" if the baby had wheezy or whistling in the chest at a time when he / she did not have a cold.

Question 9d.

"During what month did your child's chest first sound wheezy or whistling?"

_____ month ____ year

Please record the month and year during which the child's chest first sounded wheezy or whistling. The respondent may indicate the child's age at which the child's chest first sounded wheezy or whistling. The interviewer should record the month and year of the event.

Here the month and year, rather than the age, that the symptoms began is recorded in an effort to avoid confusion regarding chronologic and corrected ages.

The next 4 questions use similar phrases and the same response options. Please emphasize the phrases which are unique in each question ("on average" or "worst two week period", "daytime" or "nighttime"). If the respondent gives the same response to 5e as 5f, please confirm with the respondent that 5e refers to "on average" and that 5f refers to the "worst two week period".

Question 9e1.

*"Over the past 6 months, **on average**, how often has your child's chest sounded wheezy or whistling during the daytime? Would you say never, twice a week, more than 2 times a week, but not every day, every day, but not all the time, everyday, all the time."*

Record response. Interviewer may repeat the choices or help respondent settle upon the choice.

Question 9e2.

*"Over the past 6 months, **on average**, how often has your child's chest sounded wheezy or whistling during the nighttime? Would you say never, twice a week, more than 2 times a week, but not every day, every day, but not all the time, everyday, all the time."*

Record response. Interviewer may repeat the choices or help respondent settle upon the choice.

Question 9f1.

*"Over the past 6 months, **during the worst 2 week period,** how often has your child's chest sounded wheezy or whistling during the daytime? Would you say never, twice a week, more than 2 times a week, but not every day, every day, but not all the time, everyday, all the time."*

Record response. Interviewer may repeat the choices or help respondent settle upon the choice.

Question 9f2.

*"Over the past 6 months, **during the worst 2 week period,** how often has your child's chest sounded wheezy or whistling during the nighttime? Would you say never, twice a week, more than 2 times a week, but not every day, every day, but not all the time, everyday, all the time."*

Record response. Interviewer may repeat the choices or help respondent settle upon the choice.

Question 9g.

"Since our last contact with you, has your child taken any medicine prescribed by a doctor for wheezing?"

Record "Yes" or "No".

Question 10.

"Since our last contact with you, has your child had a cough when he/she did not have a cold?"

Record whether the baby coughs when otherwise well. Do not include coughing associated with eating, drinking or choking. See question 9 for clarification of phrase "cold".

Question 10a.

"At what time of the day has this cough usually occurred? In the morning; shortly after rising; later in the day; during the night; no relation to time of day?"

Interviewer should read all responses to the respondent and circle all that apply.

Question 10b.

"Has he/she coughed on most days for as much as 2 to 3 months?"

Please record "Yes" or "No"

Question 10c.
"During what month did your child first develop the cough?"
Record month and year that the cough first developed, when the respondent recognized the cough whether or not they view it as a problem.

Question 10d.
"Has your child's chest ever sounded wheezy or whistling with episodes of coughing?"
Record yes if the respondent associates wheezing or whistling breath sounds with the presence of the cough.

Questions 10e1-10f2. Questions 10e1-10f2 are completed similarly to questions 9e1-9f2.

Question 11.
*"Over the past 6 months, **on average**, how many **days per month** did you have to change your daytime or evening plans because of your child's breathing problems:"*
Please record the number of days that the respondent reports having to change plans because the baby's breathing is different from baseline. An example of a changed plan includes withholding the baby from a planned daycare or babysitting situation because he / she is wheezing.

This does not include preventive avoidance, such as avoiding social situations or trips because the baby might get sick or may be exposed to another child. The interviewer may assist the respondent in selecting a number by establishing a range, then having the respondent select a specific answer.

Question 12.
*"Over the past 6 months, **during the worst 2 week period**, how many **days** did you have to change for daytime or evening plans because of your child's breathing problems:"* |___|___| # of days
Interviewer should emphasize the "worst 2 week period". Record response using criteria similar to those in Question 11.

The next 4 questions relate to respiratory diagnoses that may be associated with wheezing and airway dysfunction, either directly, as secondary symptom or as a condition that may be confused with airway dysfunction.

Question 13.
"Since our last contact with you, has your child had asthma or reactive airways disease diagnosed by a doctor?"
Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 14.
"Since our last contact with you, has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?"

Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 15.
"Since our last contact with you, has your child had croup diagnosed by a doctor?"
Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Script: "The next question are about your baby's diet....."

Question 16.
"In the past 6 months, did your baby receive mother's breast milk, either at breast, from a bottle or through a tube?"
If baby received any breast milk, record "Yes".

If yes to Question 16, answer question 16a and 16b, if "No", skip to Question 17:

Question 16a.
"For how many months did your child receive breast milk? Would you say? ....Less than 1 month, 1-3 months, 4-6 months?"
Record duration of time that the baby received any breast milk.

Question 16b.
"For how many months did your child receive breast milk <u>for more than half of his/her feedings</u>? Would you say... Less than 1 month, 1-3 months, 4-6 months?"

Record duration of time that the baby received more than ½ of feedings from breast milk, provided by any route.

A mother who fed her infant breast milk 25% of the time and formula 75% of the time, weaning the baby at 4 months, would answer "yes" to question 16, "4-6 months" to question 16a, and "less than 1 month" to question 16b.

Script: "***The next questions are about smoke exposure.....***"

Question 17.
*"Which of the following 3 statements best describes the situation regarding smoking in your child's **home?**..... Read all options to the interviewee before recording a response: Smoking is allowed in any common room of the home, smoking is limited to part of the house where the child rarely goes, there is no smoking inside at all?"*

Question 17a.
If answer to question 17 is "there is no smoking inside at all", then ask question 17a,
"Are there any exceptions to this situation?"
If respondent reports any exceptions, record "Yes". If no, skip to question 18.

Question 17b.
If answer to 17a is "Yes", then ask question17b.

"Under what circumstances are the exceptions allowed?"
Record a brief response as free text.

Question 18.
"*Which of the following 5 statements best describes the situation regarding smoking in your* ***car?****.... Read all options to the interviewee before recording a response: Smoking is usually or always allowed, smoking is sometimes allowed, smoking occurs in the car only when the child is not inside, there is no smoking inside the car"*

Record the response as it applies to the main automobile in which the baby rides. If family does not ride in a car (public transportation only or baby doesn't leave home), record response #1.

Question 18a and 18b. Responses questions to 18a and 18b are completed similarly to questions 17a and 17b.

Question 19.
'How often has the mother or primary caregiver smoked since your child was born?'

If speaking with the mother, please substitute "you" for "mother or primary caregiver". Record response based on occurrence of any smoking activity, regardless of where it takes place. Record "Never" if the mother or primary care giver has never smoked anywhere since the baby was born, record "Daily" if she /he smokes daily in any location, and record "Occasionally" if response is neither "Never" nor "Daily".

Question 20.
"How many people in the child's home smoke?" |___|___| people

Record response based on occurrence of any smoking activity, regardless of where it takes place.

Script: *"The next questions are about your home and your babysitter's home or day care"*

Question 21.
"Approximately how many hours per week does your child spend at a babysitter's home or day care?" |___|___| hrs If 0 skip to question 22.

Record the number of hours that the baby spends outside his/her home, regardless of whether this is in the home of another parent, grandparent, or friend.

Question 21a.
If response to question 21 is greater than 0,
"How frequent is there smoke exposure at the babysitter or daycare?"

Record response based on occurrence of any smoking activity, regardless of where it takes place. Record never if there is no smoking allowed inside the babysitter or daycare provider's edifice in any location, record daily if smoking occurs inside the edifice daily in any location, and record occasionally if response is neither never nor daily.

Question 21b.
"How many children beside your baby are in the daycare?"

Record the average number of children less than 12 years of age who inhabited the babysitter or daycare over the past 2 weeks when the baby was present.

Question 22.
"How many children under 12 live in your house?" |___|___| children
Record number of children who spend more than 7 nights in the home over a two week period.

Question 23.
"Do you have any pets inside the home?"
Record "Yes" or "No"

Question 23a. If yes record,
"How many dogs? Cats? Do you have other pets? What kinds? How many?"

If respondent reports pets, please record the number of dogs and cats separately. Group all other pets together and record total number of pets that are neither a dog nor a cat.

Script: "*The last questions involve respiratory treatments that your baby may receive.....*"

Question 24.
"Has your child had RSV shots (palivizumab) to prevent Respiratory Syncytial Virus (Synagis, palivizumab, RSV shot)?"
Record respondent's answer, "Yes", "No" or "Don't know". If respondent does not recognize the treatment, record "Don't Know".

Question 25.
"Has your child had a flu shot?"
Record respondent's answer, "Yes", "No" or "Don't know". If respondent does not recognize the vaccine, record "Don't Know".

Question 26.
"Is your child on any oxygen therapy at home?"
Record respondent's answer, "Yes" or "No". If respondent does not know, the interviewer should prompt further by asking, "does your baby use any oxygen equipment, such as an oxygen tank, at home?"

Question 26a – 26c.
These questions can be answered using the following script.

If response to question 26 is "Yes",
"What device is used to provide the oxygen?.....Oxygen hood, nasal cannula or ventilator?"
Record response in checkbox provided.

If response to question 26 is "Yes", the interviewer should ask,
"*What percent oxygen does your baby use?"*

Record response as fraction inspired oxygen (FiO2) in the space adjacent to the oxygen delivery device. For example, room air (ambient air) is 21% oxygen, enter as FiO2 value of 0.21

If response to question 26 is either "nasal cannula" or "oxygen hood", interviewer asks, *"How many liters of oxygen does the baby receive?"*

Record value as liters per minute (1cc is .001liters, 1/8 liter is 0.125 liters, ¼ liter is 0.25 liters, etc.)

MEDICATIONS

Script: *"The last two questions involve the medicines your child is taking for breathing problems....."*

Question 27.
"What medicines has your baby taken over the past 6 months, including medicines delivered by a nebulizer or breathing machine?"

For this question, record all respiratory related medications. Record a written response in the table and later, after the interview, record the medication code from the table below. Medications that do not appear on the list are unlikely to be used to treat respiratory conditions in this age group. Do not prompt for each medication in the medication list.

Chapter 8
18-22 Month Questionnaire

Introduction

The purpose of this questionnaire is to obtain an **interval** respiratory history and to identify a history of atopy that may increase the likelihood of symptomatic airway dysfunction. Questions are designed to ascertain the frequency and severity of wheezing and cough episodes and to assess the need for outpatient pulmonary care. In addition, risk factors obtained at the 1st interview will be confirmed. There are a total of 30 questions, encompassing questions from the discharge, 6 month and 12 month questionnaires.

This interview will be conducted at 18-22 months' corrected age, either by the local NICHD Follow Up Program (Option 1) or long distance from Rochester (Option 2), based on center preference.

Instructions for Completing the 18-22 Month Questionnaire (SUPF03)
Timing of the Interview:
The target window for this interview is between 18 and 22 months' corrected age. If for any reason the infant is enrolled into the Pulmonary Outcome Study at this time window or becomes available for a Pulmonary Outcomes Interview outside this window, the questionnaire should be administered, collecting an interval history from the time of NICU discharge or the most recent interview, whichever is most recent.

This interview should be administered by a certified study interviewer either by telephone prior to the regularly scheduled 18-22 month NICHD developmental follow-up clinic visit or face to face at the time of the visit.

Heading- Infant's Identification
The following information is included in the heading section of all patient specific data forms: Center, Site, Network Number, SUPPORT Follow-up Number, Birth Number and Mother's Initials **(optional).** This information should be completed on the first page of the interview and the SUPPORT Follow-up Number written on subsequent pages in case the completed form pages are separated.

8.1 Conducting the Interview

8.1.1 Initiating the interview:

The 18-22 month questionnaire is conducted in the same fashion as for the 6 and 12 month interviews. In addition to the 27 questions included in the 6 and 12 month questionnaires, the 18-22 month questionnaire includes 7 questions about allergies.

See Chapter 8 of the manual of procedures for directions to administer questions 1-28 of the 18-22 month questionnaire. Directions for questions 28-34 begin here.

Script: "*The last questions regard allergies.....*"

Question 28.

*"**During the past year**, for how many days has your child been unable to do his/her usual activities because of illnesses such as chest (not head) colds, bronchitis, asthma or pneumonia? 0-3 per year, 4-5 per year, 6-9 per year, more than 9 per year?"*

Question 29.

*"How many head colds (common colds) **per year** does your child usually have? Would you say…0-3 per year, 4-5 per year, 6-9 per year, more than 9 per year?"*

Question 30.

*"Has your child **ever** had hay fever or any other condition that makes his/her nose runny, stuffy, or itchy **apart** from colds?"*

Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 31.

*"Has your child **ever** had allergies which cause nose, eye or lung problems?"*

Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 32.

*"Has your child **ever** been allergic to any food?"*

Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 33.

*"Has he/she **ever** been allergic to any medicine?"*

Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 34.

*"Has your child **ever** had eczema (allergic skin rash)?"*

Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No".

Question 34a.

If Question 34 is "Yes",

"Was this diagnosed by a doctor?"

Record response, "Yes" or "No"

APPENDIX A
List of Acronyms

BOOST Trial – Benefits of Oxygen Saturation Targeting
BPD – Bronchopulmonary Dysplasia
CA – Corrected Age
CLD – Chronic Lung Disease
CPAP – Positive pressure applied with a face mask to help keep lungs inflated
FEF – Forced Expiratory Flow
GA – Gestational Age
GDB – Generic Data Base for the NICHD Neonatal Research Network
HDMA – House Dust Mite Allergen
HIPPA – Health Insurance Portability and Accountability Act of 1996
HSR Group – University of Rochester Health Services Research Group
IRB – Institutional Review Board
LBW – Low Birth Weight
NBW – Normal Birth Weight
NHLBI Consensus Expert Report -
NICHD – The National Institute of Child Health and Human Development
NICU – Neonatal Intensive Care Unit
PFT – Pulmonary Function Testing
RDS – Respiratory Distress Syndrome
ROP – Retinopathy of Prematurity
RSV - Respiratory Syncytial Virus
SUPPORT Trial– The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants
UKOS – The United Kingdom Oscillator Study
VLBW – Very Low Birth Weight

APPENDIX B
FOLLOW-UP STUDY FORMS

SUPF01 **NICU Discharge-Baseline Interview**

SUPF02 **6 Month Interview and 12 Month Interview**

SUPF03 **18-22 Month Interview**

Insert Forms

APPENDIX C

Appendix E - Revised 9-1-05

SAMPLE CONSENT FORMS

SAMPLE CONSENT FORM FOR PATIENTS ENROLLED IN SUPPORT

TITLE: SUPPORT Trial Pulmonary Outcomes Study- Follow-up Study of Infants Enrolled in the NICHD Neonatal Research Network SUPPORT Trial

PRINCIPAL INVESTIGATOR: Timothy P. Stevens, MD MPH

CO-PRINCIPAL INVESTIGATOR: Dale L. Phelps, MD

INTRODUCTION and BACKGROUND:
This consent form describes a research study and what you may expect if you decide to have your infant participate. You are encouraged to read this consent form carefully and to ask the person who presents it any questions you may have before making your decision whether or not to have your infant participate.

This form describes the known possible risks and benefits in the study. You are completely free to choose whether to participate.

Your infant is invited to be a part of this research project because (s)he is a premature baby who is a member of the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network SUPPORT Trial. As described in the SUPPORT Trial Consent that was discussed with you previously, the SUPPORT Trial is designed to find out more about treatment with CPAP (positive pressure applied with a face mask to help keep the lungs inflated) and learn the appropriate levels of oxygen saturation (oxygen levels in the blood) in premature babies. The SUPPORT Study will determine the effect of these treatments on your baby's respiratory and visual health prior to discharge from the Neonatal Intensive Care Unit (NICU).

However, we know that many babies born as early as your baby are at risk for breathing problems, especially wheezing and coughing during early childhood, after discharge from the NICU.

PURPOSE:
The purpose of Pulmonary Outcomes Study described here is to determine the effect of the SUPPORT Study treatment on your baby's respiratory health in early childhood, during the first 18-22 months after his/her expected delivery at full term.

PROCEDURES:
You and your infant's participation will begin with an interview before your infant is discharged from the hospital or at the time of your regular follow-up visit with the NICU Outpatient Clinic. At this interview we will ask you questions about your family, including questions about family history of breathing problems, and questions about your home, including things that may

increase your child's risk of breathing problems. You do not need to answer any questions that make you uncomfortable. The interview will take about 15 minutes.

We will continue to stay in touch with you and your infant by telephone or in person at one of your visits (((**Customize language here based on which option your center chose for administering the questionnaires**))) every 6 months over the next 18-22 months, a total of three times. At these times, we will ask questions about your child's breathing (especially wheezing and coughing), medication use, and visits to a Doctor, Emergency Room, or Hospital visits for treatment of breathing problems. We will also ask you several questions about your family and yourself. The entire call should take about 15 minutes of your time, less if your baby has had no breathing problems.

We will schedule the telephone calls at a time that is convenient for you. The telephone calls will occur when your infant is 6, 12, and 18 months after his/her expected delivery at full term.

The results from your baby's questionnaire will be combined with other infants from around the country. However, your baby's name will not be used.

We also ask your permission to contact your baby's Doctor to obtain their assessment of your baby's breathing and need for breathing treatments.

NUMBER OF PARTICIPANTS:
All babies who participate in the SUPPORT Trial will be offered the opportunity to participate in this study. There will be close to 1300 infants enrolled in the SUPPORT Trial. We hope that as many as possible will choose to participate in this study to help determine the long-term effect of the SUPPORT Study treatments. Approximately 40 babies will be enrolled locally.

RISKS AND DISCOMFORTS:
You may experience anxiety or psychological discomfort while completing these questionnaires and/or the interviews. You are free to choose not to answer any question for any reason.

BENEFITS:
The major benefit to you and your infant is that actual or potential breathing problems experienced by your baby could be identified early and brought to the attention of your baby's Doctor for treatment.

CONFIDENTIALITY OF RECORDS AND HIPAA AUTHORIZATION
While we will make every effort to keep information we learn about you private, this cannot be guaranteed. Other people may need to see the information. While they normally protect the privacy of the information, they may not be required to do so by law. Results of the research may be presented at meetings or in publications, but your name will never be used.

The federal Health Insurance Portability and Accountability Act (HIPAA) requires us to get your permission to use health information about you that we either create or use as part of the research. This permission is called an Authorization. We will use your child's research record, related information from your child's medical records, results of laboratory and other diagnostic tests obtained during his/her initial hospitalization, as well as the information and test results obtained during the telephone interviews of your baby's breathing.

We will use your child's health information to conduct the study, to monitor your child's respiratory status and to determine long term effects on breathing of the SUPPORT Study treatments. Health information is used to report results of research to sponsors and federal regulators. It may be audited to make sure we are following regulations, policies and study plans. If you have never received a copy of the Strong Health HIPAA Notice, please ask the investigator for one. To meet regulations or for reasons related to this research, the study investigator may share a copy of this consent form and records that identify you with the following people: The Department of Health and Human Services, the University of Rochester, the NICHD Neonatal Research Network and organizations (like RTI International) used by NICHD to manage studies.

If you decide to have your child take part, your Authorization for this study will not expire unless you cancel or revoke it. You can always cancel this Authorization by writing to the study investigator. If you cancel your Authorization, your child will be removed from the study. However, standard medical care and any other benefits to which you are otherwise entitled will not be affected. Canceling your Authorization only affects uses and sharing of information after the study investigator gets your written request. Information gathered before then may need to be used and given to others. For example, information gathered during your child's initial hospitalization will be sent to the NICHD Neonatal Research Network and to RTI International.

As stated in the section on Voluntary Participation below, you can also refuse to sign this consent/Authorization and not be part of the study. You can also tell us you want to leave the study at any time without canceling the Authorization. By signing this consent form, you give us permission to use and/or share your health information.

COSTS:
There is no cost to you to participate in the study.

CONTACT PERSONS:
For more information about this research, or if you believe your infant has suffered a research-related injury, please contact Timothy P. Stevens, MD MPH or Dale L. Phelps, MD (Principal Investigators) at (585) 275-2972. You can also reach them, or one of the other attending physicians, by asking the unit secretary in the NICU to page them.

If you have any questions about your rights as a research subject, you may contact the Human Subjects Protection Specialist at the University of Rochester Research Subjects Review Board at Box 315, 601 Elmwood Avenue, Rochester, NY 14642-8315. Telephone: (585) 276-0005, for long-distance you may call toll-free, (877) 449-4441.

VOLUNTARY PARTICIPATION:
Taking part in this study is entirely voluntary. You are free not to participate or to withdraw at any time, for whatever reason, without risking loss of present or future care you would otherwise expect to receive. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

SIGNATURES/ DATES:

I have read (or have had read to me) the contents of this permission form and have been

encouraged to ask questions. I have received answers to my questions. I give permission for my child to participate in this study. I will receive a signed copy of this form for my records and future reference.

_____
Study Subject (Print)

_____	_____	_____
Parent/Guardian Signature	Print Name	Date

PERSON OBTAINING CONSENT

I have read this form to the parent/guardian of this subject and/or the parent/guardian of this subject has read this form. An explanation of the research was given and questions from the subject's family were solicited and answered to their satisfaction. In my judgment, the parent/guardian has demonstrated comprehension of the information. I will provide the parent/guardian with signed copy of this consent form.

_____	_____	_____
Signature, person conducting Informed Consent	Print Name	Date

SAMPLE CONSENT FORM FOR FUTURE SUPPORT PATIENTS

Consent to Act as a Research Subject

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial of the NICHD Neonatal Research Network

Neil Finer, MD, his associates, and the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network are conducting a research study to find out more about treatment with CPAP (positive pressure applied with a face mask to help keep the lungs inflated) and learn the appropriate levels of oxygen saturation (oxygen levels in the blood) in premature babies. You are being asked to allow your child to be in the study because there is a possibility he/she will be born between 16 and 12 weeks early (24-28 weeks gestational age).

The purposes of this trial are the following:
1) To compare infants who receive delivery room CPAP and who have strict guidelines for having a breathing tube placed with infants who have the tube placed and surfactant (a liquid which helps babies with immature lungs breath easier by helping keep their lungs from collapsing) given in the delivery room.
2) To compare low range (85-89%) oxygen saturation levels with high range (91-95%) levels to determine if a lower range results in decreased ROP (Retinopathy of Prematurity, an eye disease that may result in impairment of vision or even blindness, which may be caused by excessive levels of oxygen.)

Duration of the Study: We expect to include about 1300 babies in the study from all the NICHD Neonatal Research Network hospitals over a two-year period.

The use of CPAP and Intubation/Surfactant are both treatments currently used in the delivery room at UCSD. The decision as to which to use is currently made by the physician attending the delivery.

The oxygen level currently used in the NICU at UCSD is between 85% and 95%. Both treatment groups (85-89% and 91-95%) fall within that range. The study will attempt to keep babies in one of these two smaller ranges.

If you agree to allow your child to be in this study, the following will happen to your child: Prior to delivery, and after your permission, your baby will be randomized (chosen by chance like the flip of a coin) to one of two lung treatment strategies. The treatments are as follows:
1) CPAP in the delivery room immediately after birth and continuing in the NICU, or
2) The placement of a tube in his/her trachea (windpipe) in the delivery room followed by surfactant administration and ventilation (breathing for the baby using a machine).

In addition to being randomly assigned to one of the two groups described above, your baby will be randomized to a High reading or Low reading oximeter (a monitor that displays how

much oxygen is in the blood). The oximeters (oxygen monitors) used in this trial are FDA approved oximeters which have been modified for research purposes. This modification makes the monitors show a value which is either slightly higher or slightly lower than the true oxygen level when values are between 85 and 95%. Outside those ranges, the oximeter works the same as the standard of care device.

Which group your baby is randomized to will not be known to the nurse taking care of your baby, or his/her physician. Only the study coordinator will know which group your baby is in. Within the range of oxygen which we normally keep babies in, your baby will either be on the high end of normal or the low end of normal. He/she will remain on this device until he/she reaches 36 weeks adjusted age. (e. g. 24 wks gestation plus 12 weeks of age = 36 weeks adjusted age). Other care will be conducted as normal during his/her participation in the study.

We will continue to stay in touch with you and your infant by telephone or in person at one of your visits ((((Customize language here based on which option your center chose for administering the questionnaires)))) every 6 months over the next 18-22 months, a total of three times. At these times, we will ask questions about your child's breathing (especially wheezing and coughing), medication use, and visits to a Doctor, Emergency Room, or Hospital for treatment of breathing problems. We will also ask you several questions about your family and yourself. The entire call should take about 15 minutes of your time, less if your baby has had no breathing problems.

We will schedule the telephone calls at a time that is convenient for you. The telephone calls will occur when your infant is 6, 12, and 18 months after his/her expected delivery at full term.

The results from your baby's questionnaire will be combined with other infants from around the country. However, your baby's name will not be used.

Participation in this study may involve some added risks or discomforts. Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby. Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted ventilation (methods to help them breathe). If the attending physician deems this necessary, participation in the study will not affect this decision. Some unknown risks may be learned during the study. If these occur, you will be informed by the study personnel. The only other risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential. There will be no name or other patient identification in any study report that may be published after the study is completed. Measures taken to protect you and your baby's identity are described in the confidentiality section of this document.

There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen near discharge) or wheezing in the first 2 years and/or a decrease in the need for eye surgery as a result of exposure to oxygen. Because we do not know in advance the actual strategies chosen for your child, or which of the treatment strategies is the most effective, it is also possible that your baby will receive no direct benefit. The knowledge learned from this study may help us treat babies in the future. However, as noted above, each of the 4 possible combinations of treatments is considered by some units to represent their desired approach.

If your child is injured as a direct result of participation in this research, the University of California will provide any medical care your child needs to treat those injuries. The University will not provide any other form of compensation to you if your child is injured. You may call the UCSD Human Research Protections Program office at (858) 455-5050 for more information about this, or to inquire about your rights as a research subject, or to report research-related problems.

_____ has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Wade Rich, the Study Coordinator, or Renee Bridge, the Research Nurse, at 619-543-6560. You may contact the principal investigator Dr. Neil Finer at 619-543-3794

As an alternative to participation in this study you may decide to have your baby's doctor decide which treatment your baby will receive. If you decide not to include your child in this study, none of his/her medical information will be included in the study data. Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care your child will receive at this institution of other loss of benefits to which your child is entitled. If you withdraw your child from the study, the attending physician will decide whether to maintain current treatment or change it, based on your child's needs at the time of the decision. Data collection for research purposes will stop at that time.

Clinical information will be collected from your baby's chart by study personnel at UCSD. Information will be labeled with a code number. Coded information will be sent to the NICHD Neonatal Network's Data Coordinating Center at RTI International in Research Triangle Park, North Carolina. The study log linking the code number with your baby's identity will be kept under lock and key at UCSD. Information directly identifying your baby will not leave UCSD. Research records will be kept confidential to the extent provided by law.

You may withdraw your child from the study for any reason. In addition, the study doctors may decide to withdraw your child if they feel it is in his/her best interest to do so. You have received a copy of this consent document to keep and the Experimental Subject's Bill of Rights.

You agree to have your child participate.

_____
Parent's or legal guardian's signature DATE

_____
Relationship of legal guardian to subject DATE

_____
Signature of person explaining and getting consent DATE

APPENDIX D
RELATIONSHIP CODES

The following codes are used to identify the primary caretaker.

001 - Mother of Child
002 - Father of Child
011 - Husband, Significant Other (SO)(if different from 002)
012 - Wife, Girlfriend (if different from 001)
021 - Maternal grandmother
022 - Paternal (SO) grandmother
031 - Maternal grandfather
032 - Paternal (SO) grandfather
041 - Maternal aunt
042 - Paternal (SO) aunt
051 - Maternal uncle
052 - Paternal (SO) uncle
061 - Brother
062 - Step Brother
071 - Sister
072 - Step Sister
081 - Maternal female cousin
082 - Paternal (SO) female cousin
091 - Maternal male cousin
092 - Paternal (SO) male cousin
101 - Other maternal relative
102 - Other paternal (SO) relative
201 - Foster mother
202 - Foster father
301 - Adoptive mother
302 - Adoptive father
401 - Other non-relative
402 - Social worker/case worker
501 - Staff in congregate care
502 - Still hospitalized
504 - Unknown

APPENDIX E
BREATHING DIARY

APPENDIX F
CONTACT INFORMATION TEMPLATE

All centers (Option 1 and 2 centers) will track their own patient's telephone and contact information for the purpose of administering telephone questionnaires at 6, 12 and 18-22 months.

The following core set of contact information is recommended for all enrolled patients.

For option 2 centers, use template to fax or email patient contact information to the Rochester site.

Network number: _____

Patient Name: First _____ Last: _____

Nickname: *(If relevant)* _____

DOB: __ __ / __ __ / __ __ __ __

Gender: Male Female

Name of Prior Interview Respondent (Primary Respondent)

Primary Respondent Contact Information

Name: _____

Relationship to patient: _____

Mailing address: _____

_____

_____

Telephone number #1: _____

Telephone number #2: _____

Email: _____

Secondary (Backup) Caretaker Information

Name: _____

Relationship to patient: _____

Mailing address: _____

_____

_____

Telephone number #1: _____

Telephone number #2: _____

Email: _____

NICHD SUPPORT Trial
Pulmonary Outcomes Follow up Study

NICU Discharge-Baseline Interview

This interview should be administered by a trained study nurse to the parent/guardian. The target window for this interview is prior to NICU discharge or within the first 30 days following NICU discharge. For patients enrolled in the Pulmonary Outcomes Follow up Study after this target window, this interview should be performed at the time of enrollment.

This interview is for:

_____
(Child's name)

All questions pertain only to his/her health.

N.B. Parents or guardians expressing concerns regarding their child's breathing should be advised to discuss them with the family's primary care physician.

Introduction to the Study:
Premature babies are more likely than full term babies to have breathing problems after discharge from the NICU. The purpose of this study is to see whether or not the treatment your baby received as part of the SUPPORT Study improves your baby's breathing in the 18-22 months following the baby's due date.

As part of this study, we will contact you every 6 months or so to ask you questions about your baby's breathing. The questions will be about your baby's breathing symptoms, especially wheezing and coughing, and about your baby's need for medical visits and treatments for breathing problems.

Wheezing can mean different sounds to different people. By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical.

We have prepared a diary for you to help you keep track of your baby's breathing, especially breathing problems and treatments.

Give diary

To complete the diary, please record how often your baby has wheezing or coughing, whether your baby visited a doctor's office, emergency room or was hospitalized for breathing problems and what medications your baby needs. When we call, we'd like you to gather the diary and any medications or other information about your baby's breathing.

In order to help us understand your baby's breathing and risk for breathing problems at home, we'd like to ask you a few questions about your home and about whether breathing problems run in the family. As with all information we collect, the answers to these questions will be kept confidential.

NICU Discharge-Baseline Interview

Center: ___ Site: ___ Network No. ____ SUPPORT Follow-up No. _____ Birth No. ___ Mother's Initials: ___

1. Child's Name_____ _____ (first) (last) 2.Today's Date: |__|__| - |__|__| - |__|__|__|__| mm dd yyyy

3. Child's Sex: 1~ Male 2~ Female

4. Child's Birthdate: |__|__| - |__|__| - |__|__|__|__| mm dd yyyy

Enter name and relationship code of the person being interviewed.

5a. Name: _____ _____ 5b. Relationship Code: |__|__|__|

001 - Mother of Child
002 - Father of Child
301 - Adoptive mother
302 - Adoptive father

Other: _____
Common codes are listed here. For other relationships, please look up relationship code from Appendix B of the Follow up Manual of Procedures and enter above.

6. Type of Interview: 1~ Face to Face 2~ Telephone

At this time, we would like a little information about the environment in which your new child will grow up.

7. First, how many people normally live with you in your home for at least 6 months of the year?

Total household members: |__|__|

8. After the first few months, will your child be sharing a room with other family members on a regular basis?

1~ Yes 2~ No

8a. IF YES: How many people will sleep in the same room with him/her? |__|__|

9. How many rooms are there in your house, excluding closets and bathrooms? |__|__|

10. Do you have any pets inside the home? 1~ Yes 2~ No *Skip to Question 11*

If YES, how many.....
10a. *check and record number:* 1~ Dogs in the home? |__|__|
2~ Cats in the home? |__|__|
3~ Other pets are in the home? |__|__| SPECIFY: _____

11. Does your home or apartment have air conditioning or some kind of cooling? 1~ Yes 2~ No *Skip to Question 12*

If Yes, 11a. Air Conditioning? 1~ Yes 2~ No
11b. Evaporative Cooling? *(Desert Southwest)* 1~ Yes 2~ No
11c. Other? 1~ Yes 2~ No If YES, SPECIFY_____

12. How is your home heated? (IF MORE THAN ONE, PLEASE CHECK ALL THAT APPLY).
    - 1~ Steam or hot water (radiator)
    - 2~ Central gas furnace (furnace)
    - 3~ Electric
    - 4~ Wood Stove
    - 5~ Other SPECIFY: _____
    - 6~ Don't know

13. What one fuel is used most for cooking in your home?
    - 1~ Electricity
    - 2~ Gas
    - 3~ Fuel Oil
    - 4~ Wood Stove
    - 5~ Other SPECIFY: _____
    - 6~ Don't Know

The next questions are about your baby's diet.

14. Is your child receiving: (READ ALL CHOICES)
    - 1~ Only breast milk
    - 2~ Only formula *Skip to Question 15*
    - 3~ Both breast milk and formula *Skip to Question 15*

If answer to 14 is 1 (only breast milk)

a. Will this be supplemented with formula in the first 6 months?

1~ Yes 2~ No 2~ Don't Know

b. If yes, when will supplements begin? |___|___| months

15. Does the mother (you) plan to work outside the home within the next year?
    - 1~ Yes
    - 2~ No
    - 3~ Don't Know

The next questions are about smoke exposure.

16. Which one of the following 3 statements best describes the situation regarding smoking in your child's **home**? *Read all options to the interviewee before recording a response.*

    1❑ Smoking is allowed in any common room of the home
    2❑ Smoking is limited to part of the house where the child rarely goes
    3❑ There is no smoking inside at all → 16a. Are there any exceptions to this situation?

    1~ Yes 2~ No (Skip to Question 17)

    16b. Under what circumstances are the exceptions allowed? SPECIFY:

    _____

17. Which one of the following 5 statements best describes the situation regarding smoking in your **car**? *Read all options to the interviewee before recording a response.*
    1❑ Do not have a car
    2❑ Smoking is usually or always allowed
    3❑ Smoking is sometimes allowed
    4❑ Smoking occurs in the car only when the child is not inside
    5❑ There is no smoking inside the car → 17a. Are there any exceptions to this situation?

1~ Yes 2~ No (Skip to Question 18)

17b. Under what circumstances are the exceptions allowed? SPECIFY:

_____

18. How often has the baby's mother or primary caretaker (you) smoked since your child was born?

1~ Never 2~ Occasionally 3~ Daily

19. Altogether, how many people who live in the child's home smoke? |___|___| people

In the next section, we'd like to know what breathing and allergy problems run in the family. Administer attached Family History Questionnaire using the following script:

Mother or guardian:

We'll start with the baby's mother. How old is the baby's biologic mother? Does she have bronchitis, emphysema, COPD, bronchiectasis, asthma, inhaled allergies, or food allergies?

Does the baby's mother have any other chronic respiratory illness?

How often does this person smoke in the baby's home?

Father
For the baby's biologic father, is he living? How old is he? Does she have bronchitis, emphysema, COPD, bronchiectasis, asthma, inhaled allergies, or food allergies?

Does he have any other chronic respiratory illness?

How often does he smoke in the baby's home?

Complete the remainder of the table by collecting the same medical history using the scripting above.

20. Finally, which friend or relative is most likely to be able to contact you 6 months from now in case we lose contact with you?

_____ _____
Name Relationship

_____
Address

_____
Telephone

_____
Cell Phone

_____
Email

Family History Questionnaire

	Mother	Father	Maternal Grandmother	Maternal Grandfather	Paternal Grandfather	Paternal Grandfather
1. Relationship to enrolled child:						
2. Living?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
3. Age (in years):	_____	_____	_____	_____	_____	_____
4. Does this person have:						
a. COPD	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
b. Chronic Bronchitis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
c. Emphysema?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
d. Bronchiectasis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
e. Asthma?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
f. Inhaled Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
g. Food Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
h. Any other chronic respiratory disease? (SPECIFY)	1. Yes 2. No _____ _____	1. Yes 2. No _____ _____	1. Yes 2. No _____ _____	1. Yes 2. No _____ _____	1. Yes 2. No _____ _____	1. Yes 2. No _____ _____
j. Check if respondent has no knowledge of medical history?	~	~	~	~	~	~
5. How often does this person smoke in the baby's home*?	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently

Never = never; rarely = less than once per month; sometimes = once per month but less than once /week; frequently = once per week or greater
Thank you for your help in providing us with this important information, and for your continued participation in the Pulmonary Follow up Study.

NICHD SUPPORT Trial
Pulmonary Outcomes Follow up Study

Administered At 6 And 12 Months Corrected Age

This interview should be administered by a trained study interviewer for:

_____
(Child's name)

All questions pertain only to his/her health.

The parent or care giver, who completed the initial interview, should complete this survey and all future surveys. The interviewer will need to ask for that parent (see Manual of Operations).

Introduction Script:
When parent or primary care giver is on phone:

Hello, my name is <your name>. I am calling from the <NICHD Center>. As you probably remember, when you were in the NICU you enrolled in our study about respiratory health of premature infants. I am calling to ask you some questions about your baby's breathing. It will take about 10-20 minutes to complete. Is this a good time for you?

As with all information we collect, the answers to these questions will be kept confidential.

Before we begin this interview, it would be helpful if you could gather your breathing diary and any medications your child has been prescribed or has been taking and have them in front of you.

1. TODAY'S DATE: |__|__| - |__|__| - |__|__|__|__|
mm dd yyyy

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's Name:_____ _____
(first) (last)

Child's Birthdate: |__|__| - |__|__| - |__|__|__|__|
mm dd yyyy

Telephone Number _____-_____-_____

Address _____

_____

Which friend or relative is most likely to be able to contact you 6 months from now in case we lose contact with you?

_____ _____
Name Relationship

_____
Address

_____
Telephone

_____
Cell Phone

_____
Email

Enter name and relationship code of the person being interviewed:

2a. Name: _____ _____ 2b. Relationship Code: |__|__|__|

001 - Mother of Child
002 - Father of Child
301 - Adoptive mother
302 - Adoptive father

Other: _____
Common codes are listed here for other relationships, please look up relationship code from Appendix B of the Follow up Manual of Procedures and enter above.

3. Type of Interview: 1~ Face to Face 2~ Telephone

4. Location of Interviewer: 1~ Local Center (Option 1) 2~ Rochester (Option 2)

Instructions:
Parents or guardians expressing concerns regarding their child's breathing should be advised to discuss them with the family's primary care physician.

Where the phrase "last contact" is used below, please substitute with the most specific relevant time prompt, e.g. for the 6 month interview, refer to "since NICU discharge"; for the 12 month interview, refer to "over the past 6 months", etc.

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (__ __) months ago on (__ __/__ __/__ __) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing problems your child may have.

5. Has the child been with you during the past 6 months? 1~ Yes 2~ No

Since our last contact with you about your child.....

6. How many times has your child visited a doctor's office? |___|___| times

6a. How many of these times were because of wheezing or breathing problems? |___|___| times

Since our last contact with you about your child.....

7. How many times has your child visited an Emergency Department (Emergency room)? |___|___| times

7a. How many of these times were because of wheezing or breathing problems? |___|___| times

Since our last contact with you about your child.....

8. How many times has your child stayed in the hospital for one or more nights in a row? |___|___| times

8a. How many of these times were because of wheezing or breathing problems? |___|___| times

The next questions are about your baby's breathing.
The first question is about wheezing. By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical.

9. Since our last contact with you, has your baby's chest sounded wheezy or whistling?

1~ Yes 2~ No 3~ Don't know

Question 9a. "Has your baby's breathing sounded like this?" ***(play audio clip of wheezing).***

1~ Yes 2~ No 3~ Don't know If 2 or 3, SKIP TO QUESTION 10

IF **YES** TO QUESTION 9 or 9a:

9b. Has this occurred with colds?

1~ Yes
2~ No *Skip to c*
3~ Sometimes

9c. Has your child's chest sounded wheezy or whistling apart from colds?

1~ Yes
2~ No

9d. During what month did your child's chest first sound wheezy or whistling?

|___|___|months (enter calendar month, Jan = 01; Feb = 02); |___|___| Year

9e. Over the past 6 months, **on average**, how often has your child's chest sounded wheezy or whistling during:

The Daytime? Would you say...(e.1)

1❑ Never
2❑ Twice a week
3❑ More than two times a week, but not every day
4❑ Everyday, but *not* all the time
5❑ Everyday, all the time

The Nighttime? Would you say...(e.2)

1❑ Never
2❑ Once every two weeks or less
3❑ Once a week
4❑ More than 1 night a week
5❑ Frequently/Every night

9f. Over the past 6 months, **during the worst 2 week period**, how often has your child's chest sounded wheezy or whistling during:

The Daytime? Would you say... (f.1)

1❑ Never
2❑ Twice a week
3❑ More than two times a week, but not every day
4❑ Everyday, but *not* all the time
5❑ Everyday, all the time

The Nighttime? Would you say...(f.2)

1❑ Never
2❑ Once every two weeks or less
3❑ Once a week
4❑ More than 1 night a week
5❑ Frequently/Every night

9g. Since our last contact with you, has your child taken any medicine prescribed by a doctor for wheezing?

1~ Yes
2~ No

IF YES, BE SURE TO COMPLETE QUESTION 27

10. Since our last contact with you, has your child had a cough when he/she did not have a cold?

1~ Yes 2~ No SKIP TO QUESTION 11

IF **YES** TO QUESTION 10

10a. At what time of the day has this cough usually occurred?
(CHECK ALL THAT APPLY)

1~ In the morning, shortly after rising
2~ Later in the day
3~ During the night
4~ No relation to time of day

10b. Has he/she coughed on most days for as much as 2 to 3 months?

1~ Yes
2~ No

10c. During what month and year did your child first develop the cough?

|___|___|months (enter calendar month, Jan = 01; Feb = 02); |___|___| Year

10d. Has your child's chest ever sounded wheezy or whistling with episodes of coughing?

1~ Yes
2~ No

10e. Over the past 6 months, **on average**, how often has your child had coughing during:

The Daytime? Would you say... (e.1)	***The Nighttime? Would you say...(e.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

10f. Over the past 6 months, **during the worst 2-week period**, how often has your child had coughing?

The Daytime? Would you say... (f.1)	***The Nighttime? Would you say...(f.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

11. Over the past 6 months, **on average**, how many **days per month** did you have to change your daytime or evening plans because of your child's breathing problems: |___|___| # of days

12. Over the past 6 months, **during the worst 2 week period**, how many **days** did you have to change for daytime or evening plans because of your child's breathing problems: |___|___| # of days

13. Since our last contact with you, has your child had asthma or reactive airways disease diagnosed by a doctor?
1~ Yes 2~ No

14. Since our last contact with you, has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?
1~ Yes 2~ No

15. Since our last contact with you, has your child had croup diagnosed by a doctor?
1~ Yes 2~ No

The next questions are about your baby's diet.

16. In the past 6 months, did your baby receive mother's breast milk, either at breast, from a bottle or through a tube?

1~ Yes 2~ No If NO, skip to Question 17

If yes to Question 16:

16a. For how many months did your child receive breast milk feedings?
Would you say... 1~ Less than 1 month
2~ 1-3 months
3~ 4-6 months

16b. For how many months did your child receive breast milk for more than half of his/her feedings?
Would you say... 1~ Less than 1 month
2~ 1-3 months
3~ 4-6 months

The next questions are about smoke exposure.

17. Which one of the following 3 statements best describes the situation regarding smoking in your child's **home**? *Read all options to the interviewee before recording a response.*
1❑ Smoking is allowed in any common room of the home
2❑ Smoking is limited to part of the house where the child rarely goes
3❑ There is no smoking inside at all → 17a. Are there any exceptions to this situation?

1~ Yes 2~ No (Skip to Question 18)

17b. Under what circumstances are the exceptions allowed? SPECIFY:

_____

18. Which one of the following 5 statements best describe the situation regarding smoking in your **car**? *Read all options to the interviewee before recording a response.*
1❑ Do not have a car
2❑ Smoking is usually or always allowed
3❑ Smoking is sometimes allowed
4❑ Smoking occurs in the car only when the child is not inside
5❑ There is no smoking inside the car → 18a. Are there any exceptions to this situation?

1~ Yes 2~ No (Skip to Question 19)

18b. Under what circumstances are the exceptions allowed? SPECIFY:

_____

19. How often has the **mother or primary care giver** smoked since your child was born?

1~ Never 2~ Occasionally 3~ Daily

20. How many people in the child's home smoke? |___|___| people

The next questions are about your home and your babysitter's home or day care.

21. Approximately how many hours per week does your child spend at a babysitter's home or day care?
|___|___| hrs *If 0, skip to Question 22*

___IF 21 is greater than 0:

21a. How frequent is there smoke exposure at the babysitter or daycare?

1~ Never 2~ Occasionally 3~ Daily 4~ Don't Know

21b. How many children beside your baby are in the daycare? |___|___|___| children

22. How many children under 12 live in your house? |___|___| children

23. Do you have any pets inside the home? 1~ Yes 2~ No *Skip to Question 24*

23a. If YES, how many pets are there inside the home?
Check all that apply and record number: 1~ Dogs |___|___|
2~ Cats |___|___|
3~ Other |___|___| SPECIFY: _____

The last questions involve respiratory treatments that your baby may receive.

PROPHYLAXIS

24. Has your child had RSV shots to prevent Respiratory Syncytial Virus (Synagis, palivizumab, RSV shot)?

1~ Yes 2~ No 3~ Don't know

25. Has your child had a flu shot? 1~ Yes 2~ No 3~ Don't know

OXYGEN

26. Is your child on any oxygen therapy at home?

1~ Yes 2~ No Skip to Question 27

Indicate Yes or No for each			*lpm = liters per minute
26a. Oxygen cannula	1~ Yes	2~ No FiO2_____	lpm*_____
26b. Oxygen hood	1~ Yes	2~ No FiO2_____	lpm*_____
26c. Ventilator	1~ Yes	2~ No FiO2_____	lpm*_____

MEDICATIONS *(Enter responses in table. Do not prompt for each medication in the Medication Code List below.)*

The last two questions involve the medicines your child is taking for breathing problems.

27. What medicines is your baby taking, including medicines delivered by a nebulizer or breathing machine at home?	27a. Code	27b. Does he/she take that medicine everyday, sometimes or only when sick? *(repeat for each medication)*
1		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
2		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
3		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
4		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
5		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
6		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
7		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

Medication Code List:

Rescue medicines:
1 Albuterol
2 Proventil
3 Serevent
4 Ventolin
5 Volmax
6 Xopenex

Inhaled medications:
7 Cromolyn (Intal)
8 Nedocromil (Tilade)

Inhaled steroids:
9 Advair
10 Aerobid
11 Azmacort
12 Beclovent
13 Flovent
14 Vanceril
15 Pulmicort

Systemic steroids:
16 Decadron
17 Prednisone

Leukotriene blocker:
18 Accolate
19 Singulair

Methylxanthines:
20 Theophylline

Diuretic medications:
21 Diuril
22 Lasix
23 Aldactizide
24 Aldactone

Miscellaneous / Non-specific
25 Nebulizer
26 Other_____

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Pulmonary Follow Up Study. Please continue to keep your baby's breathing diary up to date.

NICHD SUPPORT Trial
Pulmonary Outcomes Follow up Study

Administered At 18-22 Months Corrected Age

This interview should be administered by a trained study interviewer. The target window for this interview is between 8-22 months' corrected age.

_____
(Child's name)

All questions pertain only to his/her health.

Introduction Script:
When parent or primary care giver is on phone:

Hello, my name is <your name>. I am calling from the <NICHD Center>. As you probably remember, when you were in the NICU you enrolled in our study about respiratory health of premature infants. I am calling to ask you some questions about your baby's breathing. It will take about 10-20 minutes to complete. Is this a good time for you?

As with all information we collect, the answers to these questions will be kept confidential.

Before we begin this interview, it would be helpful if you could gather your breathing diary and any medications your child has been prescribed or has been taking and have them in front of you.

1. TODAY'S DATE: |__|__| - |__|__| - |__|__|__|__|
mm dd yyyy

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's Name:_____ _____
(first) (last)

Child's Birthdate: |__|__| - |__|__| - |__|__|__|__|
mm dd yyyy

Telephone Number _____-_____-_____

Address _____

_____

Which relative is most likely to have your address in case we lose contact with you?

_____ _____
Name Relationship

_____
Address

_____
Telephone

_____
Cell Phone

_____
Email

Enter name and relationship code of the person being interviewed*:

2a. Name: _____ _____ 2b. Relationship Code: |__|__|__|

001 - Mother of Child
002 - Father of Child
301 - Adoptive mother
302 - Adoptive father

Other: _____
Common codes are listed here for other relationships, please look up relationship code from Appendix B of the Follow up Manual of Procedures and enter above.

3. Type of Interview: 1~ Face to Face 2~ Telephone

4. Location of Interviewer: 1~ Local Center (Option 1) 2~ Rochester (Option 2)

Instructions:
Parents or guardians expressing concerns regarding their child's breathing should be advised to discuss them with the family's primary care physician.

Where the phrase "last contact" is used below, please substitute with the most specific relevant time prompt, e.g. for the 18-22 month interview, refer to "over the past 6 months", etc.

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (__ __) months ago on (__ __/__ __/__ __) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing problems your child may have.

5. Has the child been with you over the past 6 months? 1~ Yes 2~ No

Since our last contact with you about your child...

6. How many times has your child visited a doctor's office? |__|__| times

6a. How many of these times were because of wheezing or breathing problems? |__|__| times

Since our last contact with you about your child...

7. How many times has your child visited an Emergency Department (Emergency room)? |__|__| times

7a. How many of these times were because of wheezing or breathing problems? |__|__| times

Since our last contact with you about your child...

8. How many times has your child stayed in the hospital one or more nights in a row? |__|__| times

8a. How many of these times were because of wheezing or breathing problems? |__|__| times

The next questions are about your baby's breathing.

The first question is about wheezing. By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical. It can sound like this,..... (play audio clip of wheezing).

9. Since our last contact with you, has your baby's chest sounded wheezy or whistling?

1~ Yes 2~ No 3~ Don't know If 2 or 3, SKIP TO QUESTION 10

Question 9a. "Has your baby's breathing sounded like this?" ***(play audio clip of wheezing).***

1~ Yes 2~ No 3~ Don't know If 2 or 3, SKIP TO QUESTION 10

IF **YES** TO QUESTION 9 or 9a:

9b. Has this occurred with colds?

1~ Yes
2~ No *Skip to c*
3~ Sometimes

9c. Has your child's chest sounded wheezy or whistling apart from colds?

1~ Yes
2~ No

9d. During what month and year did your child's chest first sound wheezy or whistling?

|___|___|months (enter calendar month, Jan = 01; Feb = 02); |___|___| Year

9e. Over the past 6 months, **on average**, how often has your child's chest sounded wheezy or whistling during:

The Daytime? Would you say...(e.1)	***The Nighttime? Would you say...(e.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

9f. Over the past 6 months, **during the worst 2 week period**, how often has your child's chest sounded wheezy or whistling during:

The Daytime? Would you say... (f.1)	***The Nighttime? Would you say...(f.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

9g. Since our last contact with you, has your child taken any medicine prescribed by a doctor for wheezing?

1~ Yes
2~ No

10. Since our last contact with you, has your child had a cough when he/she did not have a cold?

1~ Yes 2~ No SKIP TO QUESTION 11

IF **YES** TO QUESTION 10

10a. At what time of the day has this cough usually occurred?
(CHECK ALL THAT APPLY)

1~ In the morning, shortly after rising
2~ Later in the day
3~ During the night
4~ No relation to time of day

10b. Has he/she coughed on most days for as much as 2 to 3 months?

1~ Yes
2~ No

10c. During what month and year did your child first develop the cough?

|___|___|months (enter calendar month, Jan = 01; Feb = 02); |___|___| Year

10d. Has your child's chest ever sounded wheezy or whistling with episodes of coughing?

1~ Yes
2~ No

10e. Over the past 6 months, **on average**, how often has your child had coughing during:

The Daytime? Would you say... (e.1)	***The Nighttime? Would you say...(e.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

10f. Over the past 6 months, **during the worst 2-week period**, how often has your child had coughing?

The Daytime? Would you say... (f.1)	***The Nighttime? Would you say...(f.2)***
1❑ Never	1❑ Never
2❑ Twice a week	2❑ Once every two weeks or less
3❑ More than two times a week, but not every day	3❑ Once a week
4❑ Everyday, but *not* all the time	4❑ More than 1 night a week
5❑ Everyday, all the time	5❑ Frequently/Every night

11. Over the past 6 months, **on average**, how many **days per month** did you have to change your daytime or evening plans because of your child's breathing: |___|___| # of days

12. Over the past 6 months, **during the worst 2 week period**, how many **days** did you have to change for daytime or evening plans because of your child's breathing: |___|___| # of days

13. Since our last contact with you, has your child had asthma or reactive airways disease diagnosed by a doctor?
1~ Yes 2~ No

14. Since our last contact with you, has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?
1~ Yes 2~ No

15. Since our last contact with you, has your child had croup diagnosed by a doctor?
1~ Yes 2~ No

The next question are about your baby's diet.

16. In the past 6 months, did your baby receive mother's breast milk, either at breast, from a bottle or through a tube?

1~ Yes 2~ No If NO, skip to Question 17

If yes to Question 16:

16a. For how many months did your child receive breast milk feedings?
Would you say... 1~ Less than 1 month
2~ 1-3 months
3~ 4-6 months

16b. For how many months did your child receive breast milk for more than half of his/her feedings?
Would you say... 1~ Less than 1 month
2~ 1-3 months
3~ 4-6 months

The next questions are about smoke exposure.

17. Which one of the following 3 statements best describes the situation regarding smoking in your child's **home**? *Read all options to the interviewee before recording a response.*
1❑ Smoking is allowed in any common room of the home
2❑ Smoking is limited to part of the house where the child rarely goes
3❑ There is no smoking inside at all → 17a. Are there any exceptions to this situation?

1~ Yes 2~ No (Skip to Question 18)

17b. Under what circumstances are the exceptions allowed? SPECIFY:

_____

18. Which one of the following 5 statements best describes the situation regarding smoking in your **car**? *Read all options to the interviewee before recording a response.*
1❑ Do not have a car
2❑ Smoking is usually or always allowed
3❑ Smoking is sometimes allowed
4❑ Smoking occurs in the car only when the child is not inside
5❑ There is no smoking inside the car → 18a. Are there any exceptions to this situation?

1~ Yes 2~ No (Skip to Question 19)

18b. Under what circumstances are the exceptions allowed? SPECIFY:

_____

19. How often has the **mother or primary care giver** smoked since your child was born?

1~ Never 2~ Occasionally 3~ Daily

20. How many people in the child's home smoke? |___|___| people

The next questions are about your home and your babysitter's home or day care.

21. Approximately how many hours per week does your child spend at a babysitter's home or day care?
|___|___| hrs If 0 skip to question 22.

IF 21 is greater than 0:

21a. How frequent is there smoke exposure at the babysitter or daycare?

1~ Never 2~ Occasionally 3~ Daily 4~ Don't Know

21b. How many children beside your baby are in the daycare? |___|___|___| children

22. How many children under 12 live in your house? |___|___| children

23. Do you have any pets inside the home? 1~ Yes 2~ No Skip to Question 24

23a. If YES, how many pets are there inside the home?
Check all that apply and record number: 1~ Dogs |___|___|
2~ Cats |___|___|
3~ Other |___|___| SPECIFY: _____

The last questions involve respiratory treatments that your baby may receive.

PROPHYLAXIS

24. Has your child had RSV shots to prevent Respiratory Syncytial Virus (Synagis, palivizumab RSV, shot)?

1~ Yes 2~ No 3~ Don't know

25. Has your child had a flu shot? 1~ Yes 2~ No 3~ Don't know

OXYGEN

26. Is your child on any oxygen therapy (oxygen tank) at home?

1~ Yes 2~ No Skip to Question 27

Indicate Yes or No for each				*lpm = liters per minute
a. Oxygen cannula	1~ Yes	2~ No	FiO2_____	lpm*_____
b. Oxygen hood	1~ Yes	2~ No	FiO2_____	lpm*_____
c. Ventilator	1~ Yes	2~ No	FiO2_____	lpm*_____

MEDICATIONS *(Enter responses in table. Do not prompt for each medication in the Medication Code List below.)*

The last two questions involve the medicines your child is taking for breathing problems.

27. What medicines is your baby taking, including medicines taken by a nebulizer or breathing machine at home?	27a. Code	27b. Does he/she take that medicine everyday, sometimes or only when sick? *(repeat for each medication)*
1		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
2		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
3		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
4		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
5		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
6		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
7		1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

Zedication Code List:

Rescue medicines:
1 Albuterol
2 Proventil
3 Serevent
4 Ventolin
5 Volmax
6 Xopenex

Inhaled medications:
7 Cromolyn (Intal)
8 Nedocromil (Tilade)

Inhaled steroids:
9 Advair
10 Aerobid
11 Azmacort
12 Beclovent
13 Flovent
14 Vanceril
15 Pulmicort

Systemic steroids:
16 Decadron
18 Prednisone

Leukotriene blocker:
18 Accolate
19 Singulair

Methylxanthines:
20 Theophylline

Diuretic medications:
21 Diuril
22 Lasix
23 Aldactizide
24 Aldactone

Miscellaneous / Non-specific
25 Nebulizer
26 Other_____

The last questions regard allergies.

28. **During the past year**, for how many days has your child been unable to do his/her usual activities because of illnesses such as chest (not head) colds, bronchitis, asthma or pneumonia?
1❑ 0-3 per year
2❑ 4-5 per year
3❑ 6-9 per year
4❑ more than 9 per year

29. How many head colds (common colds) **per year** does your child usually have? Would you say...
1❑ 0-3 per year
2❑ 4-5 per year
3❑ 6-9 per year
4❑ more than 9 per year

30. Has your child **ever** had hay fever or any other condition that makes his/her nose runny, stuffy, or itchy **apart** from colds? 1~ Yes 2~ No

31. Has your child **ever** had allergies which cause nose, eye or lung problems?
1~ Yes 2~ No

32. Has your child **ever** been allergic to any food?
1~ Yes 2~ No

33. Has he/she **ever** been allergic to any medicine?
1~ Yes 2~ No

34. Has your child **ever** had eczema (allergic skin rash)?
1~ Yes 2~ No (End of Interview)

34a. Was eczema diagnosed by a doctor?

QUESTION

1~ Yes 2~ No

End of Interview THANK YOU FOR YOUR COOPERATION

From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Navarrete, Cristina; Everett, Ruth
Subject: FW: SUPP_GRO 01 form.doc
Date: Thursday, October 13, 2005 10:47:21 AM
Attachments: SUPP_GRO 01 form.doc

Hi Rose,

Please take a look at the data collection form that Cristina came up with. She took the Glutamine data collection form that many of the coordinators are already familiar with and modified it so that the anthropometric data and nutrrition data are on the same sheet. Much of the anthropometric data are already collected for GDB at some of the listed time points, but I recall from our last meeting that the coordinators preferred to have all data for a particular study on the same sheet. Ruth helped us with the sheet and thought it should meet coordinator needs - 1 sheet per baby per day of data collection.

Hope it looks OK to you. What do we do next - does she need a working group? If she does, I would suggest Richard, Brenda, Seetha (who has expressed an interest in the IUGR sub-group) and Neil. Also, when do we need the Manual of Operations by? The Savannah meeting? Ruth pulled out our premie board - its not bad ... a fairly light plexiglass gizmo about 6 inches wide and 24 inches long which she will bring to GA for the demo.

We are very excited to be starting and hope some good information comes out of the effort

Shahnaz
-----Original Message-----
From: Navarrete, Cristina
Sent: Wednesday, October 05, 2005 10:55 PM
To: Duara, Shahnaz
Subject: RE: SUPP_GRO 01 form.doc

How's this?

From: Duara, Shahnaz
Sent: Wed 10/5/2005 4:58 PM
To: Navarrete, Cristina
Subject: SUPP_GRO 01 form.doc

Hi Tina,

Not bad - could you knock off the highlighted sections at the bottom? I don't think route or supplements are critical and will only annoy people if we collect data unlikely to be used.

SD

<<SUPP_GRO 01 form.doc>>

Center _ _ _ Site _ Network No. _ _ Mother's Initials _ _ _, _ _ Birth No. _ _

This form should be completed on **days 1, 7, 14, 21 and 28, corrected ages 32 wks & 36 wks or discharge.**

1. Date: _ _/ _ _/ _ _ _ _ **2. Day of Life: _ _ _**

3. Today's new weight **_ _ _ _ gm**
4. Today's new length **_ _ . _ cm**
5. Today's new HC **_ _ . _ cm**

A. Parenteral Nutritional Intake
1. Was there parenteral intake? Y N
If Yes,

2. PN	% Dextrose	AA ordered (gm/kg/day)	PN volume received (cc)	% Lipid soln	Intralipid volume received (cc)
a. Today's 1st Bag	_ _ . _	_ . _	_ _ _ . _	_ _	_ _ . _
b. Today's 2nd Bag	_ _ . _	_ . _	_ _ _ . _	_ _	_ _ . _
c. Today's 3rd Bag	_ _ . _	_ . _	_ _ _ . _	_ _	_ _ . _

B. Enteral Intake
1. Was there enteral intake? Y N
If Yes, please record information below:

	Type	Caloric Density (kcal/oz)	volume received (cc)	nutrient additives
1.	_ _ _	_ _	_ _ _ . _	_ _ _ _
2.	_ _ _	_ _	_ _ _ . _	_ _ _ _
3.	_ _ _	_ _	_ _ _ . _	_ _ _ _
4.	_ _ _	_ _	_ _ _ . _	_ _ _ _

Enteral Nutrition Key	
Type: 00= none 01= breast milk (full strength) 02= Similac Special Care 03= Enfamil Premature Formula 04= Similac (regular term infant formula) 05= Enfamil (regular term infant formula) 06= Pregestimil 07= Nutramigen 08= Alimentum 09= Prosobee 10= Isomil 11= Similac 60/40 12= Similac Natural Care 13= Neosure 14= Enfamil 22 15= Other 16= Pedialyte	Nutrient Additives: 2= MCT or other oil 4= polycose 6= human milk fortifier 8= formula powder or liquid 9= Promod 7= other

Initials of person completing this form _ _ _

From: Wade Rich
To: "Hastings, Betty J."; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SAE-Support
Date: Thursday, October 13, 2005 9:18:56 AM
Attachments: (b) (6)Medwatch.pdf

Sorry guys. Here it is. The question still applies.
wade

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, October 12, 2005 2:53 PM
To: 'Higgins, Rosemary (NIH/NICHD)'; 'Hastings, Betty J.'; 'Zaterka-Baxter, Kristin'
Subject: SAE-Support

Attached is a support MedWatch. The one on line can be filled out. Is it OK to use it if I identify the study in the Patient Identifier section?
wade

U.S. Department of Health and Human Services

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

FDA USE ONLY

Triage unit sequence #

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: / Date of Birth:	3. Sex	4. Weight
(b) (6) SUPPORT Trial In confidence	1 Days / or / (b) (6)	☐ Female ☒ Male	____ lbs or 0.890 kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☒ **Adverse Event** and/or ☐ **Product Problem** *(e.g., defects/malfunctions)*

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
- ☒ Death (b) (6) *(mo/day/yr)*
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☐ Disability
- ☐ Congenital Anomaly
- ☐ Required Intervention to Prevent Permanent Impairment/Damage
- ☐ Other: _____

3. **Date of Event** *(mo/day/year)*: (b) (6)

4. **Date of This Report** *(mo/day/year)*: (b) (6)

5. **Describe Event or Problem**

27 +2 week infant twin. 890 grams BW. Required bag/mask ventilation in the delivery room, but was stabalized and transported to NICU on CPAP. Maintained on CPAP for approx. 15 hours. At that time the infant was intubated for increased FiO2 and CO2 in the 70's. At the time of the intubation breath sounds were noted to be decreased on the right side. An X-Ray confirmed a R pneumothorax, which was aspirated with a butterfly needle. CO2 and oxygen saturation slowly improved. At approx. 19 hours of age the infant started to deteriorate with increasing FiO2 levels and CO2. Blood gas values were pH 7.02 CO2 98 PO2 58 Base Excess -8, and FiO2 77 on high frequency ventilation. Transillumination of the chest showed a reaccumulated pneumothorax, and a Chest Tube was placed. Copious amounts of blood were seen to be coming from the chest tube. CT surgery was called but did not arrive in time. The infant was given atropine and epinepherine. At 04:35 the infant died.

6. **Relevant Tests/Laboratory Data, Including Dates**

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

C. SUSPECT MEDICATION(S)

1. **Name** *(Give labeled strength & mfr/labeler, if known)*
#1
#2

2. Dose, Frequency & Route Used	3. Therapy Dates *(If unknown, give duration)* from/to (or best estimate)
#1	#1
#2	#2

4. **Diagnosis for Use** *(Indication)*
#1
#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # *(if known)*	7. Exp. Date *(if known)*
#1	#1
#2	#2

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. **NDC#** *(For product problems only)*
- -

10. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. **Brand Name**

2. **Type of Device**

3. **Manufacturer Name, City and State**

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mo/day/yr)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. **If Implanted, Give Date** *(mo/day/yr)*

7. **If Explanted, Give Date** *(mo/day/yr)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?** ☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

10. **Device Available for Evaluation?** *(Do not send to FDA)* ☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mo/day/yr)*

11. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

1. Name and Address	Phone #
wrich@ucsd.edu	619-543-5375

2. Health Professional?	3. Occupation	4. Also Reported to:
☒ Yes ☐ No	Research Coord.	☐ Manufacturer ☒ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☐

PLEASE TYPE OR USE BLACK INK

FDA Mail to: **MEDWATCH** 5600 Fishers Lane Rockville, MD 20852-9787 -or- **FAX to:** 1-800-FDA-0178

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

5. **Describe Event or Problem** *(continued)*

6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Concomitant Medical Products and Therapy Dates *(Exclude treatment of event) (continued)*

ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:

- Medications *(drugs or biologics)*
- Medical devices *(including in-vitro diagnostics)*
- Special nutritional products *(dietary supplements, medical foods, infant formulas)*
- Cosmetics
- Medication errors

Report product problems - quality, performance or safety concerns such as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labeling
- Therapeutic failures

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- Death
- Life-threatening *(real risk of dying)*
- Hospitalization *(initial or prolonged)*
- Disability *(significant, persistent or permanent)*
- Congenital anomaly
- Required intervention to prevent permanent impairment or damage

Report even if:

- You're not certain the product caused the event
- You don't have all the details

How to report:

- Just fill in the sections that apply to your report
- Use section C for all products except medical devices
- Attach additional blank pages if needed
- Use a separate form for each patient
- Report either to FDA or the manufacturer *(or both)*

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise.

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Important numbers:

- 1-800-FDA-0178 -- To FAX report
- 1-800-FDA-1088 -- To report by phone or for more information
- 1-800-822-7967 -- For a VAERS form for vaccines

To Report via the Internet:

http://www.fda.gov/medwatch/report.htm

The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
MedWatch; HFD-410
5600 Fishers Lane
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

OMB statement:
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FORM FDA 3500 (12/03) (Back) **Please Use Address Provided Below -- Fold in Thirds, Tape and Mail**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES OR APO/FPO

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH
The FDA Safety Information and Adverse Event Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

General Instructions for Completing the MedWatch Form FDA 3500

For use by health professionals and consumers for voluntary reporting of adverse events and product problems with medications (drugs or biologics, **except vaccines**), medical devices (including in vitro diagnostics), special nutritional products (dietary supplements, infant formulas, medical foods) and other FDA-regulated medical products. Events involving vaccines should be reported to the Vaccine Adverse Event Reporting System (VAERS) (http://www.fda.gov/cber/vaers/report.htm).

Note for consumers: If possible, please take the 3500 form to your health professional (e.g., doctor or pharmacist) so that information based on your medical record that can help in the evaluation of your report will be provided. If, for whatever reason, you do not wish to have your health professional fill out the form, you are welcome to do so yourself.

GENERAL INSTRUCTIONS

- Please make sure that all entries are either typed, printed in a font no smaller than 10 point, or written using black ink.
- Please complete all sections that apply to your report.
- To complete an item when information is not available, use the following as appropriate:
  - NA for not applicable
  - NI for no information at this time (but may become available later)
  - UNK for unknown
- Dates should be entered as month/day/year (e.g., June 3, 1998 = 06/03/1998).
  If exact dates are unknown, please provide the best estimate.
- For narrative entries, if the fields do not provide adequate space, attach an additional page(s) as needed.
- If the case report involves more than two (2) suspect medications or devices, please submit another copy of FDA Form 3500, with only **Section C** or **Section D** filled in as appropriate.
- **Section C** (Suspect medication(s)) may be used to report on special nutritional products such as dietary supplements as well as drugs or biologics.
- If your report involves a serious adverse event with a device and it occurred in a facility other than a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.
- Please incorporate the following specific information:
  - Identify all attached pages as Page __ of __
  - Indicate the appropriate section and block number next to the narrative continuation
  - Include the phrase continued at the end of each field that has additional information continued onto another page

If you have further questions about completing this form, call MedWatch at: 1-800-FDA-1088.

SECTION A: PATIENT INFORMATION

Complete a separate form for each patient, unless the report involves a medical device where multiple patients were adversely affected through the use of the same device. In that case, please indicate the number of patients in block B5 (Describe event or problem) and complete Section A and blocks B2, B5, B6, B7, and D11 for each patient. Enter the corresponding patient identifier in block A1 for each patient involved in the event.

When a newborn baby is found to have a congenital anomaly that the initial reporter considers possibly associated with a product administered to the mother during pregnancy, the patient is the newborn baby.

Parent-child/fetus report(s) are those cases in which either a fetus/suckling infant or the mother, or both, sustain an adverse event that the initial reporter considers possibly associated with a product administered to the mother during pregnancy. Several general principles are used for filing these reports:

- If there has been no event affecting the child/fetus, report only on the parent. For those cases describing fetal demise or spontaneous abortion, only a parent report is applicable
- When only the child/fetus has an adverse reaction/event (other than spontaneous abortion/ fetal demise), the information provided in section A applies to the child/fetus, and characteristics concerning the parent who was the source of exposure to the product is to be provided in section C
- If both the parent and the child/fetus sustain adverse events, two reports should be provided and linked using the narrative
- For devices, one form can be used in this circumstance

A1: Patient identifier

Please provide the patient's initials or some other type of identifier that will allow you, the reporter, to readily locate the case if you are contacted for more information. **Do not use the patient's name or social security number**.

The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law.

If no patient was involved (such as may be the case with a product problem), enter none.

A2: Age at time of event or Date of birth

Provide the most precise information available. Enter the patient's birthdate, if known, or the patient's age at the time of event onset. For age, indicate time units used (e.g., years, months, days).

- If the patient is 3 years or older, use years (e.g., 4 years)
- If the patient is less than 3 years old, use months (e.g., 24 months)
- If the patient is less than 1 month old, use days (e.g., 5 days)
- Provide the best estimate if exact age is unknown

A3: Sex

Enter the patient's gender. If the adverse event is a congenital anomaly, report the sex of the child.

A4: Weight

Indicate whether the weight is in pounds (lbs) or kilograms (kgs). Make a best estimate if exact weight is unknown.

SECTION B: ADVERSE EVENT OR PRODUCT PROBLEM

B1: Adverse event *and/or* Product problem

Choose the appropriate box. Both boxes should be checked if a product problem may have caused or contributed to the adverse event.

Adverse event: Any incident where the use of a medication (drug or biologic), at any dose, a medical device (including *in vitro* diagnostics) or a special nutritional product (e.g., dietary supplement, infant formula or medical food) is suspected to have resulted in an adverse outcome in a patient.

To report, it is not necessary to be certain of a cause/effect relationship between the adverse event and the use of the medical product(s) in question. Suspicion of an association is sufficient reason to report. Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Please limit your submissions to those events that are serious. An event is classified as serious when the patient outcome is:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability
- Congenital anomaly
- Required medical or surgical intervention to prevent permanent impairment or damage

Please see instructions for block **B2** for further information on each of these criteria.

While voluntary MedWatch reporting with Form 3500 is designed for serious reports only, you are welcome to report even if your case does not meet any of these specific criteria and you feel strongly that FDA should review the report. In that situation, you should check the other box and specify the reason for reporting, including patient outcome, in the space provided. The actual narrative of the event should be entered in block **B5**.

Product problem (e.g., defects/malfunctions): Any report regarding the quality, performance, or safety of any medication, medical device or special nutritional product. In addition, please select this category when reporting device malfunctions that could lead to a death or serious injury if the malfunction were to recur.

Product problems include, but are not limited to, such concerns as:

- Suspected contamination
- Questionable stability
- Defective components
- Therapeutic failures
- Product confusion (caused by name, labeling, design or packaging)
- Suspected super potent or subpotent medication
- Labeling problems caused by printing errors/ omissions

B2: Outcomes attributed to adverse event: Indicate all that apply to the reported event:

Death: Check only if you suspect that the death was an outcome of the adverse event, and include the date if known.

Do not check if:

- The patient happened to die while using a medical product, but there was no suspected association between the death and the use of the product
- A fetus is aborted because of a congenital anomaly, or is miscarried

Life-threatening: Check if suspected that:

- The patient was at substantial risk of dying at the time of the adverse event

  or

- Use or continued use of the device or other medical product might have resulted in the death of the patient

Hospitalization (initial or prolonged): Check if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

Do not check if:

- A patient in the hospital received a medical product and subsequently developed an otherwise nonserious adverse event, unless the adverse event prolonged the hospital stay

Do check if:

- A patient is admitted to the hospital for one or more days, even if released on the same day
- An emergency room visit results in admission to the hospital
- Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage)

Disability: Check if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions. Such would be the case if the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Congenital anomaly: Check if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

Required intervention to prevent permanent impairment or damage: Check if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

(continued on next page)

SECTION B: ADVERSE EVENT OR PRODUCT PROBLEM *(continued)*

Drugs and Biologics: This box should be checked for important medical events that may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other serious outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Other: Check only if the other categories are not applicable to the event. Briefly describe the patient outcome in the space provided. The actual narrative of the event will be entered in block **B5**.

B3: Date of event

Provide the actual or best estimate of the date of first onset of the adverse event. If day is unknown, month and year are acceptable. If day and month are unknown, year is acceptable.

When a newborn baby is found to have a congenital anomaly, the event onset date is the date of birth of the child

When a fetus is aborted because of a congenital anomaly, or is miscarried, the event onset date is the date pregnancy is terminated

If information is available as to time during pregnancy when exposure occurred, indicate that information in narrative block **B5**.

B4: Date of this report

The date the report is filled out.

B5: Describe event or problem

For an **adverse event**:

Describe the event in detail, including a description of what happened and a summary of all relevant clinical information (medical status prior to the event; signs and/or symptoms; differential diagnosis for the event in question; clinical course; treatment; outcome, etc.). If available and if relevant, include synopses of any office visit notes or the hospital discharge summary. To save time and space (and if permitted by your institution), please attach copies of these records with any confidential information deleted. **Do not identify any patient, physician, or institution by name. The reporter's identity should be provided in full in section E.**

Information as to any environmental conditions that may have influenced the event should be included, particularly when (but not exclusive to) reporting about a device.

- Results of relevant tests and laboratory data should be entered in block **B6**. (See instructions for **B6**).
- Preexisting medical conditions and other relevant history belong in block B7. Be as complete as possible, including time courses for preexisting diagnoses (see instructions for B7).

If it is determined that reuse of a medical device labeled for single use may have caused or contributed to an adverse patient outcome, please report in block **B5** the facts of the incident and the perceived contribution of reuse to the occurrence.

For a **product problem**:

Describe the problem (quality, performance, or safety concern) in sufficient detail so that the circumstances surrounding the defect or malfunction of the medical product can be understood.

- If available, the results of any evaluation of a malfunctioning device and, if known, any relevant maintenance/service information should be included in this section
- For a medication or special nutritional product problem, please indicate if you have retained a sample that would be available to FDA

B6: Relevant tests/laboratory data, including dates

Please provide all appropriate information, including relevant negative test and laboratory findings, in order to most completely convey how the medical work-up/ assessment led to strong consideration of medical product-induced disease as etiology for clinical status, as other differential diagnostic considerations were being eliminated.

Please include:

- Any relevant baseline laboratory data prior to the administration or use of the medical product
- All laboratory data used in diagnosing the event
- Any available laboratory data/engineering analyses (for devices) that provide further information on the course of the event

If available, please include:

- Any pre- and post-event medication levels and dates (if applicable)
- Synopses of any relevant autopsy, pathology, engineering, or lab reports

If preferred, copies of any reports may be submitted as attachments, with all confidential information deleted. **Do not identify any patient, physician or institution by name.** The initial's reporter's identity should be provided in full in section E.

B7: Other relevant history, including preexisting medical conditions

If available, provide information on other known conditions in the patient (e.g. hypertension, diabetes mellitus, renal/hepatic dysfunction), significant history (e.g. allergies, pregnancy history, smoking, and alcohol use, drug abuse, etc.) and/or race and ethnicity.

SECTION C: SUSPECT MEDICATION(S)

For **adverse event reporting**:

A suspect medication is one that you suspect is associated with the adverse event. In block **C10** enter other concomitant medical products (drugs, biologics, medical devices, etc.) that the patient was using at the time of the event but which you do not think were involved in the event.

Up to two (2) suspect medications may be reported on one form (#1=first suspect product, #2=second suspect product). Attach an additional form if there were more than two suspect medications for the reported adverse event.

For **product problem reporting**:

A suspect medication is the product that is the subject of the report. A separate form should be submitted for each individual product problem report.

Identification of the labeler/distributor and pharmaceutical manufacturer (if known) and labeled strength of the product is important for prescription or non-prescription products.

This section may also be used to report on special nutritional products (e.g., dietary supplements, infant formula or medical foods) or other products regulated by FDA.

If reporting on a special nutritional or a drug product problem, please attach labeling/ packaging if available.

If reporting on a special nutritional only, please provide directions for use as listed on the product labeling.

C1: Name

Use the trade name as marketed. If unknown or if no trade name, use the generic name (with the manufacturer or labeler's name, if known). For quality problem reports, please include the manufacturer's name and the labeled strength for both prescription and non-prescription products.

C2: Dose, frequency & route used

Describe how the product was used by the patient (e.g., 500 mg QID orally or 10 mg every other day IV). For reports involving overdoses, the amount of product used in the overdose should be listed, not the prescribed amount.

See **APPENDIX I** for list of Routes of Administration

C3: Therapy dates

Provide the date administration was started (or best estimate) and the date stopped (or best estimate). If no dates are known, an estimated duration is acceptable (e.g., 2 years) or if therapy was less than one day, then duration is appropriate (e.g., 1 dose or 1 hour for an IV).

C4: Diagnosis for use

Provide the indication for which the product was prescribed or used in this particular patient.

C5: Event abated after use stopped or dose reduced

If available, this information is particularly useful in the evaluation of a suspected adverse event. In addition to checking the appropriate box, please provide supporting lab tests and dates, if available, in block **B6**.

C6: Lot #

If known, include the lot number(s) with all product problem reports, or any adverse event report with a biologic or medication.

C7: Expiration date

Please include if available.

C8: Event reappeared after reintroduction

If available, this information is particularly useful in the evaluation of a suspected adverse event. In addition to checking the appropriate box, please provide supporting lab tests and dates, if available, in block **B6**.

C9: NDC #

The national drug code is requested only when reporting a drug product problem. It can be found on the product label and/or packaging. Zeros and dashes should be included as they appear on the label.

C10: Concomitant medical products and therapy dates

Information on the use of concomitant medical products can frequently provide insight into previously unknown interactions between products, or provide an alternative explanation for the observed adverse event. Please list and provide therapy dates for any other medical products (drugs, biologics, medical devices, etc.) that a patient was using at or around the time of the event. Do not include products used to treat the event.

Appendix I - ROUTES OF ADMINISTRATION

Auricular (otic) 001
Buccal 002
Cutaneous 003
Dental 004
Endocervical 005
Endosinusial 006
Endotracheal 007
Epidural 008
Extra-amniotic 009
Hemodialysis 010
Intra corpus cavernosum 011
Intra-amniotic 012
Intra-arterial 013
Intra-articular 014
Intra-uterine 015
Intracardiac 016
Intracavernous 017
Intracerebral 018
Intracervical 019
Intracisternal 020
Intracorneal 021
Intracoronary 022
Intradermal 023
Intradiscal (intraspinal) 024
Intrahepatic 025
Intralesional 026
Intralymphatic 027
Intramedullar (bone marrow) 028
Intrameningeal 029
Intramuscular 030
Intraocular 031
Intrapericardial 032
Intraperitoneal 033
Intrapleural 034
Intrasynovial 035
Intratumor 036
Intrathecal 037
Intrathoracic 038
Intratracheal 039
Intravenous bolus 040
Intravenous drip 041
Intravenous (not otherwise specified) 042
Intravesical 043
Iontophoresis 044
Occlusive dressing technique 045
Ophthalmic 046
Oral 047
Oropharingeal 048
Other 049
Parenteral 050
Periarticular 051
Perineural 052
Rectal 053
Respiratory (inhalation) 054
Retrobulbar 055
Sunconjunctival 056
Subcutaneous 057
Subdermal 058
Sublingual 059
Topical 060
Transdermal 061
Transmammary 062
Transplacental 063
Unknown 064
Urethral 065
Vaginal 066

SECTION D: SUSPECT MEDICAL DEVICE

The suspect medical device is 1) the device that may have caused or contributed to the adverse event or 2) the device that malfunctioned.

In block **D11**, report other concomitant medical products (drugs, biologics, medical devices, etc.) that the patient was using at the time of the event but which you do not think were involved in the event.

If more than one suspect medical device was involved in the event, complete all of section D for the first device and attach a separate completed section D for each additional device.

If the suspect medical device is a single use device that has been reprocessed, then the reprocessor is now the device manufacturer.

D1: Brand name

The trade or proprietary name of the suspect medical device as used in product labeling or in the catalog (e.g., Flo-Easy Catheter, Reliable Heart Pacemaker, etc.). This information may 1) be on a label attached to a durable device, 2) be on a package of a disposable device, or 3) appear in labeling materials of an implantable device. Reprocessed single use devices may bear the Original Equipment Manufacturer (OEM) brand name. If the suspect device is a reprocessed single use device enter "NA".

D2: Type of device

The generic or common name of the suspect medical device or a generally descriptive name (e.g., urological catheter, heart pacemaker, patient restraint, etc.). Please do not use broad generic terms such as "catheter", "valve", "screw", etc.

D3: Manufacturer name & address

If available, list the full name and mailing address of the manufacturer of the suspected medical device. If the answer is Block D8 is "yes", then enter the name and address of the reprocessor.

D4: Product identification number/expiration date

If available, provide any or all identification numbers associated with the suspect medical device exactly as they appear on the device or device labeling. This includes spaces, hyphens, etc.

Model #: The exact model number found on the device label or accompanying packaging.

Catalog #: The exact number as it appears in the manufacturer's catalog, device labeling, or accompanying packaging.

Serial #: This number can be found on the device label or accompanying packaging; it is assigned by the manufacturer, and should be specific to each device.

Lot #: This number can be found on the label or packaging material.

Expiration date (mo/day/yr): If available, this date can often be found on the device itself or printed on the accompanying packaging.

Other #: Any other applicable identification number (e.g., component number, product number, part bar-coded product ID, etc.)

D5: Operator of device

Indicate the type (not the name) of person operating or using the suspect medical device on the patient at the time of the event as follows:

Health professional = physician, nurse, respiratory therapist, etc.
Lay user/patient = person being treated, parent/ spouse/friend of the patient
Other = nurses aide, orderly, etc.

D6: If implanted, give date (mo/day/yr)

For medical devices that are implanted in the patient, provide the implant date or your best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable.

D7: If explanted, give date (mo/day/yr)

If an implanted device was removed from the patient, provide the explant date or your best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable.

D8: Is this a Single-use Device that was Reprocessed and Reused on a Patient?

Indicate "Yes" or "No".

D9: If Yes to Item No.8, Enter Name and Address of Reprocessor

Enter the name and address of the reprocessor of the single-use device. Anyone who reprocesses single-use devices for reuse in humans is the manufacturer of the reprocessed device.

D10: Device available for evaluation?

To evaluate a reported problem with a medical device, it is often critical for the manufacturer to be able to examine the suspect product. Thus, please indicate whether the device is available for evaluation.

Indicate if the device was returned to the manufacturer and, if so, the date of the return. Do not send the device to FDA.

D11: Concomitant medical products and therapy dates

Information on the use of concomitant medical products can frequently provide insight into previously unknown interactions between products, or provide an alternative explanation for the observed adverse event. Please list and provide product names and therapy dates for any other medical products (drugs, biologics, medical devices, etc.) that the patient was using at the time of the event. Do not include products used to treat the event.

SECTION E: INITIAL REPORTER

FDA recognizes that confidentiality is an important concern to health professionals in the context of adverse event reporting. The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. However, to allow for timely follow-up in serious cases, the reporter's identity may be shared with the manufacturer unless specifically requested otherwise in block E5. The FDA will not disclose the reporters identity in response to a request from the public, pursuant to the Freedom of Information Act.

E1: Name, address & phone #

Please provide the name, mailing address and phone number of the person who can be contacted to provide information on the event if follow-up is necessary. While optional, providing the contact's E-mail address and/or fax number, would be most helpful, if available. This person will also receive an acknowledgment letter from the MedWatch program.

This information is necessary for both adverse event and product problem reports.

E2: Health professional?

Please indicate whether you are a health professional (e.g., physician, pharmacist, nurse, etc.) or not. If you are not a health professional, please complete block **E3** by filling in NA.

E3: Occupation

Please indicate your occupation (particularly type of health professional), and include specialty, if appropriate.

E4: Also reported to

Please indicate whether you have also notified or submitted a copy of this report to the manufacturer and/or distributor of the product, or, in the case of medical device reports only, to the user facility (institution) in which the event occurred. This information helps to track duplicate reports in the FDA database.

E5: Release of reporter's identify to the manufacturer

In the case of a serious adverse event (see **B1**), the Agency may provide name, address and phone number of the reporter denoted in block **E1** to the manufacturer of the suspect product. If you do not want your identity released to the manufacturer, please put an X in this box.

From: Neil Finer
To: "Hastings, Betty J."; mcw3@cwru.edu; "[SCRN] Stoll, Barbara"; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wade Rich; "Nancy Newman"; "Das, Abhik"; "Zaterka-Baxter, Kristin"
Subject: RE: New Physiologic Challenge
Date: Tuesday, October 11, 2005 1:20:23 PM

Hi Betty
In order to avoid to standards, I would vote that we all change to the new Physiologic Challenge for SUPPORT and GDB
Neil Finer

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Tuesday, October 11, 2005 7:55 AM
To: mcw3@cwru.edu; nfiner@ucsd.edu; [SCRN] Stoll, Barbara; higginsr@mail.nih.gov
Cc: wrich@ucsd.edu; Nancy Newman; Das, Abhik; Zaterka-Baxter, Kristin
Subject: New Physiologic Challenge
Importance: High

We have been receiving many questions regarding the new Physiologic Challenge.

First, should every infant enrolled in SUPPORT have at least the PHY01 form completed at 36 weeks? I'm pretty sure the answer this question is yes.

However, here is the problem, we currently have versions of these forms (January 18, 2005) which were sent to the sites. These two forms have now been revised and it's my understanding that they will be implemented along with the New GDB in January. The question is, what forms should the sites be using for current enrollments into GDB and SUPPORT? Should these revised versions be sent out and implemented now?

Thanks for your help in clarifying this.
Betty

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: physiologic definition of BPD
Date: Tuesday, October 11, 2005 1:19:38 PM

Rose
In an effort to minimize additional data collection, we were going to use GDB data. We would track this in a similar fashion to GDB. I am not that concerned about this loss, but perhaps you are more aware of how often this data is not available from the GDB database.
I would follow your advice with regard to developing such a mechanism.
Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 11, 2005 8:14 AM
To: nfiner@ucsd.edu; Das, Abhik
Subject: physiologic definition of BPD

Hi Neil and Abhik
Although the physiologic definition is a secondary outcome for SUPPORT, it is not in the manual (according to the coordinators). Do we have a mechanism for tracking this (i.e. missing data on children who have reached status) PHY01 on children alive at 36 weeks??
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Neil Finer
To: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich
Cc: Neil Finer; barbara_stoll@oz.ped.emory.edu
Subject: RE: SUPPORT
Date: Monday, October 10, 2005 5:55:37 PM

Hi Rose
I spoke to Barbara
She would like the clarification added to Question number A6 under the possible answers that option #4 read "Only for randomization requirement"
I think that this may help clarify for those sites that have had difficulty in understanding this question.
Regards
Neil

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, October 10, 2005 2:41 PM
To: 'Higgins, Rosemary (NIH/NICHD)'; Wade Rich
Cc: Neil Finer
Subject: RE: SUPPORT

Hi Rose
I believe that all centers should respond as is indicated below as
"The site should code #4 if infant was intubated ONLY for study.
The site should code #2 if infant was randomized to intubation but also needed intubation for resuscitation."

We know if the infant is randomized to Surfactant or CPAP from the SUPP 02 eligibility form, and thus if a Surfactant infant requires intubation for resuscitation, this is how form SUPP 03 should be completed. We will then know at the end of the study all Surfactant infants who required intubation for resuscitation, and, in addition, any who were not intubated.
Perhaps I am missing another issue here.
Regards
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 07, 2005 6:50 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu
Subject: FW: SUPPORT

Neil and Wade - I would appreciate you weighing in on this.

Thanks
Rose

-----Original Message-----
From: Barbara Stoll [mailto:barbara.stoll@oz.ped.emory.edu]
Sent: Thursday, October 06, 2005 2:26 PM
To: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD); bkh@rti.org
Subject: SUPPORT

We are having a meeting to review SUPPORT patient charts with my team. A

basic question has arisen:

1--SUPP03--Item A6
Need to clarify reason for intubation in the manual--
After my team thought about this, we think we should code #4 if infant intubated ONLY for study.
Should code #2 if infant randomized to intubation but also needed intubation for resuscitation.

If we code #4 for all infants randomized to intubation, we lose information on reason for resuscitation on those who also needed resuscitation

Please clarify
Thanks
BJS

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
Medical Director, Children's Healthcare of Atlanta at Egleston
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

From: Roy Heyne
To: BVohr@CareNE.org; Higgins, Rosemary (NIH/NICHD) [E]; petrie@rti.org
Cc: JANET MORGAN
Subject: Pulmonary Follow-Up of Support
Date: Friday, October 07, 2005 3:03:39 PM

Has anyone received any revisions of protocol, questionnarire, or consent template from Tim Stevens pursuant to the issues raised, recommendations made, and matters agreed during his presentation/discussion several weeks ago at our meeting in Virginia? Among other things, I thought he agreed to drop the PCP chart audit, and make some modifications to the questionnaire and consent. Carolyn, I think you or Jaimie were taking notes during this discussion. What do you show as follow-up items? We were holding out taking this to our IRB until these issues are resolved. But time is running out. Thanks.

From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Navarrete, Cristina; Everett, Ruth
Subject: FW: SUPP_GRO 01 form.doc
Date: Thursday, October 06, 2005 3:10:40 PM
Attachments: SUPP_GRO 01 form.doc

Hi Rose,

Please take a look at the data collection form that Cristina came up with. She took the Glutamine data collection form that many of the coordinators are already familiar with and modified it so that the anthropometric data and nutrrition data are on the same sheet. Much of the anthropometric data are already collected for GDB at some of the listed time points, but I recall from our last meeting that the coordinators preferred to have all data for a particular study on the same sheet. Ruth helped us with the sheet and thought it should meet coordinator needs - 1 sheet per baby per day of data collection.

Hope it looks OK to you. What do we do next - does she need a working group? If she does, I would suggest Richard, Brenda, Seetha (who has expressed an interest in the IUGR sub-group) and Neil. Also, when do we need the Manual of Operations by? The Savannah meeting? Ruth pulled out our premie board - its not bad ... a fairly light plexiglass gizmo about 6 inches wide and 24 inches long which she will bring to GA for the demo.

We are very excited to be starting and hope some good information comes out of the effort

Shahnaz
-----Original Message-----
From: Navarrete, Cristina
Sent: Wednesday, October 05, 2005 10:55 PM
To: Duara, Shahnaz
Subject: RE: SUPP_GRO 01 form.doc

How's this?

From: Duara, Shahnaz
Sent: Wed 10/5/2005 4:58 PM
To: Navarrete, Cristina
Subject: SUPP_GRO 01 form.doc

Hi Tina,

Not bad - could you knock off the highlighted sections at the bottom? I don't think route or supplements are critical and will only annoy people if we collect data unlikely to be used.

SD

<<SUPP_GRO 01 form.doc>>

Center _ _ _ Site _ Network No. _ _ Mother's Initials _ _ _, _ _ Birth No. _ _

This form should be completed on **days 1, 7, 14, 21 and 28, corrected ages 32 wks & 36 wks or discharge.**

1. Date: _ _/ _ _/ _ _ _ _ **2. Day of Life: _ _ _**

3. Today's new weight **_ _ _ _ gm**
4. Today's new length **_ _ . _ cm**
5. Today's new HC **_ _ . _ cm**

A. Parenteral Nutritional Intake
1. Was there parenteral intake? Y N
If Yes,

2. PN	% Dextrose	AA ordered (gm/kg/day)	PN volume received (cc)	% Lipid soln	Intralipid volume received (cc)
a. Today's 1st Bag	_ _ . _	_ . _	_ _ _ . _	_ _	_ _ . _
b. Today's 2nd Bag	_ _ . _	_ . _	_ _ _ . _	_ _	_ _ . _
c. Today's 3rd Bag	_ _ . _	_ . _	_ _ _ . _	_ _	_ _ . _

B. Enteral Intake
1. Was there enteral intake? Y N
If Yes, please record information below:

	Type	Caloric Density (kcal/oz)	volume received (cc)	nutrient additives
1.	_ _ _	_ _	_ _ _ . _	_ _ _ _
2.	_ _ _	_ _	_ _ _ . _	_ _ _ _
3.	_ _ _	_ _	_ _ _ . _	_ _ _ _
4.	_ _ _	_ _	_ _ _ . _	_ _ _ _

Enteral Nutrition Key	
Type: 00= none 01= breast milk (full strength) 02= Similac Special Care 03= Enfamil Premature Formula 04= Similac (regular term infant formula) 05= Enfamil (regular term infant formula) 06= Pregestimil 07= Nutramigen 08= Alimentum 09= Prosobee 10= Isomil 11= Similac 60/40 12= Similac Natural Care 13= Neosure 14= Enfamil 22 15= Other 16= Pedialyte	Nutrient Additives: 2= MCT or other oil 4= polycose 6= human milk fortifier 8= formula powder or liquid 9= Promod 7= other

Initials of person completing this form _ _ _

From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: SUPPORT GROWTH SECONDARY
Date: Monday, October 03, 2005 11:27:33 PM

1
BJS"Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> writes:
>Can you give me a 1-4 choice??
>Thanks
>Rose
>
>-----Original Message-----
>From: Barbara Stoll [mailto:barbara.stoll@oz.ped.emory.edu]
>Sent: Monday, October 03, 2005 3:48 PM
>To: Higgins, Rosemary (NIH/NICHD)
>Subject: Re: FW: SUPPORT GROWTH SECONDARY
>
>Yes
>My only comment:
>Infection plays a role in growth failure, BPD and adverse ND outcome-- I
>suggest that we evaluate the added impact of infection-- enter proven
>infection into the model, etc
>BJS
>
>"Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> on Monday, October
>03, 2005 at 1:57 PM +0000 wrote:
>>Hi
>>
>>I am missing a few votes on the SUPPORT GROWTH SECONDARY STUDY. Please
>>send me your vote ASAP.
>>
>>
>>
>>Thanks
>>
>>Rose
>>
>>
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>>==========
>>
>>
>>From: Higgins, Rosemary (NIH/NICHD)
>>Sent: Tuesday, September 20, 2005 4:25 PM
>>To: Abbot Laptook (alaptook@WIHRI.org); 'Abhik Das'; 'Brenda Poindexter';
>>'Carlo Waldemar (E-mail)'; 'Charles Rosenfeld'; 'Dale Phelps'; 'Ed
>>Donovan'; 'Ehrenkranz Richard (E-mail)'; 'Jobe Alan (E-mail)'; 'Lemons
>>Jim (E-mail)'; 'Michael O'Shea'; 'Michelle Walsh'; 'Neil Finer'; 'Oh
>>William (E-mail)'; 'Poole Kenneth (E-mail)'; 'Ronald GOldberg'; 'Shahnaz
>>Duara'; 'Shankaran Seetha (E-mail)'; 'Stevenson David (E-mail)'; 'Stoll
>>Barbara (E-mail)'; 'Tyson Jon (E-mail)'; Walid Salhab (Walid Salhab)
>>Cc: 'Petrie, Carolyn'
>>Subject: SUPPORT GROWTH SECONDARY

>>
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>>HI,
>>
>>I need a vote from the PI's regarding the SUPPORT GROWTH SECONDARY
>>presented by Dr. Duara last week at the steering committee meeting.
>>
>>
>>
>>Please indicate your preference:
>>
>>1. Yes - this needs to go forward without additional funding and should
>>start now
>> 2. Yes - this needs to go forward and we should commit funds from the
>>2006 budget (this will impact the possibility of other protocols being
>>instituted)
>> 3. No - this needs to wait for the next budget period with reassessment
>>in April 2006
>> 4. No - this should not be done
>>
>>
>>
>>
>>I have attached the protocol.
>>
>>Send me your vote by September 30.
>>
>>
>>
>>Thanks
>>
>>Rose
>>
>>
>>
>>Rosemary D. Higgins, M.D.
>>
>>Program Scientist for the Neonatal Research Network
>>
>>Pregnancy and Perinatology Branch
>>
>>Center for Developmental Biology and Perinatal Medicine
>>
>>NICHD, NIH
>>
>>6100 Executive Blvd., Room 4B03B
>>
>>MSC 7510
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>>Bethesda, MD 20892
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>>(For overnight delivery, use Rockville, MD 20852)
>>

>>301-435-7909
>>
>>301-496-3790 (FAX)
>>
>>[mailto:higginsr@mail.nih.gov]higginsr@mail.nih.gov
>>
>>
>>
>
>
>
>Barbara J. Stoll, MD
>George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
>Medical Director, Children's Healthcare of Atlanta at Egleston
>Office: 404-727-2456 Fax: 404-727-5737
>barbara_stoll@oz.ped.emory.edu
>
>This message is for the designated recipient only and may contain
>privileged or confidential information. If you have received it in error,
>please notify the sender immediately and delete the original.

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
Medical Director, Children's Healthcare of Atlanta at Egleston
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privileged or confidential information. If you have received it in error,
please notify the sender immediately and delete the original.

From: Haverkos, Lynne (NIH/NICHD)
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT trial
Date: Monday, October 03, 2005 6:05:47 PM

Rose,

I made a couple little changes and released it (with the long brief title and identifying number of uNICHD-1016. Thanks for fixing it up.

Lynne

Lynne M. Haverkos, MD, MPH
Program Director,
Behavioral Pediatrics and Health Promotion Research
http://www.nichd.nih.gov/crmc/cdb/p_behave.htm
NICHD/NIH
6100 Executive Blvd. Room 4B05 MSC 7510
Bethesda, MD. 20892-7510
For Fed Ex use: Rockville, MD. 20852
phone: 301-435-6881
fax: 301-480-0230
email: haverkol@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD)
Sent: Monday, October 03, 2005 3:07 PM
To: Haverkos, Lynne (NIH/NICHD)
Subject: SUPPORT trial

Lynne
I updated everything (using Neil's password) on the SUPPORT TRIAL (uNICHD1016). If possible, let me know when the record can be released.

Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
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(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Barbara Stoll
To: sduara@miami.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT GROWTH SECONDARY
Date: Monday, October 03, 2005 3:47:41 PM

Shahanaz

I like the growth secondary a lot.
My only comment:
Infection plays a role in growth failure, BPD and adverse ND outcome. Our recent JAMA paper showed a nice association with poor growth (is nice a good word in this context). I suggest that we evaluate the added impact of infection. You could include proven sepsis in the model, etc. I would love to work on this with you.

BJS

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT GROWTH SECONDARY
Date: Monday, October 03, 2005 2:19:52 PM

Hi Rose
I vote yes, #1 now without additional funding
Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 03, 2005 10:57 AM
Subject: FW: SUPPORT GROWTH SECONDARY

Hi
I am missing a few votes on the SUPPORT GROWTH SECONDARY STUDY. Please send me your vote ASAP.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD)
Sent: Tuesday, September 20, 2005 4:25 PM
To: Abbot Laptook (alaptook@WIHRI.org); 'Abhik Das'; 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; 'Charles Rosenfeld'; 'Dale Phelps'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; 'Jobe Alan (E-mail)'; 'Lemons Jim (E-mail)'; 'Michael O'Shea'; 'Michelle Walsh'; 'Neil Finer'; 'Oh William (E-mail)'; 'Poole Kenneth (E-mail)'; 'Ronald GOldberg'; 'Shahnaz Duara'; 'Shankaran Seetha (E-mail)'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; Walid Salhab (Walid Salhab)
Cc: 'Petrie, Carolyn'
Subject: SUPPORT GROWTH SECONDARY

HI,
I need a vote from the PI's regarding the SUPPORT GROWTH SECONDARY presented by Dr. Duara last week at the steering committee meeting.

Please indicate your preference:

1. Yes – this needs to go forward without additional funding and should start now
2. Yes – this needs to go forward and we should commit funds from the 2006 budget (this will impact the possibility of other protocols being instituted)
3. No – this needs to wait for the next budget period with reassessment in April 2006
4. No – this should not be done

I have attached the protocol.
Send me your vote by September 30.

Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510

Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Das, Abhik
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP data from SUPPORT
Date: Thursday, September 29, 2005 5:29:07 PM

We just received the green light from our IRB on this; so we will move quickly on this.

Thanks

Abhik

-----Original Message-----
From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Thursday, September 29, 2005 4:21 PM
To: Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP data from SUPPORT

That would be fine, and may even be more that I need. 5X16 = 80. or maybe that's about right.

It is far more important that I see some soon and do education/update/revision early.
It would be very sad to discover problems only after all 16 centers have turned in at least 5 data sheets. (which will be a long time from now).

I would think that if you can give me about 10 (you can block center number), I can get a pretty good first impression.

I am doing a short talk on ROP coding at the coordinators GDB meeting in Nov. on the 14th. If I can learn from these dataforms, I will know better what to do for the coordinators in Nov.

Dale

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, September 29, 2005 4:06 PM
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: ROP data from SUPPORT

Dale:

Regarding your review of ROP data from SUPPORT (section C in form SUPP09 and all of form SUPP10), I am assuming that you want us to send you this data for a small randomly selected sample of children enrolled in SUPPORT (5 per site?) who have reached status. Is my understanding correct?

Thanks

Abhik

Abhik Das, Ph.D.
Senior Research Statistician

RTI International
6110 Executive Blvd., Suite 902
Rockville, MD 20852-3903
e-mail: adas@rti.org
Phone: 301-770-8214
Fax: 301-230-4646

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPP 11
Date: Thursday, September 29, 2005 12:30:24 PM

Thanks Rose
Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, September 29, 2005 7:19 AM
To: wrich@ucsd.edu
Cc: nfiner@ucsd.edu
Subject: RE: SUPP 11

I agree – that was a mistake
Thanks
Rose

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, September 29, 2005 10:17 AM
To: Higgins, Rosemary (NIH/NICHD)
Cc: nfiner@ucsd.edu
Subject: RE: SUPP 11

Rose,
This is probably fine (will check with Neil, but we should not capitalize Support, as it may confuse the issue. We don't want them to think that if they are on <500cc flow they are not in the Support trial at all.
Wade

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, September 29, 2005 6:06 AM
To: nfiner@ucsd.edu; Wade Rich
Cc: 'Zaterka-Baxter, Kristin'
Subject: RE: SUPP 11

HI, can we state :
Our definition is that ≤ 500 ml/min flow by itself, ie without oxygen, is not considered as Support **for the purposes of the trial definition**. Therefore an infant receiving such flows, 500ml/min or less, should have the study oximeter removed after 3 days.

Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, September 28, 2005 4:03 PM
To: Higgins, Rosemary (NIH/NICHD); Wade Rich
Cc: 'Zaterka-Baxter, Kristin'
Subject: RE: SUPP 11

Hi Rose
Our definition is that ≤ 500 ml/min flow by itself, ie without oxygen, is not considered as Support. Therefore an infant receiving such flows, 500ml/min or less, should have the study oximeter removed after 3 days.

Hope this helps
Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 28, 2005 12:23 PM
To: 'Neil Finer '; 'Wade RIch '
Cc: Zaterka-Baxter, Kristin
Subject: SUPP 11

Neil
For the definition in the manual for "high flow" for the technical memo: If an infant is on 500 ml or less of room air, how long does the infant stay on the study pulse oximeter (does the 3-day (72 hour) guideline apply to these infants). Bottom line is 500 ml room air nasal cannula considered support??
Kris needs this ASAP for the technical memo.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wade Rich
To: "Burnell, Erica"; Higgins, Rosemary (NIH/NICHD) [E]
Cc: nfiner@ucsd.edu; "Zaterka-Baxter, Kristin"
Subject: RE: SUPPORT Oximeters
Date: Tuesday, September 27, 2005 5:21:20 PM

Kris,

Oximeter #s 318351 and 318859 are going out from UCSD to Rocester FedEx today.

Wade

-----Original Message-----
From: Burnell, Erica [mailto:Erica_Burnell@URMC.Rochester.edu]
Sent: Tuesday, September 27, 2005 1:58 PM
To: 'Higgins, Rosemary (NIH/NICHD)'; 'wrich@ucsd.edu'
Cc: 'nfiner@ucsd.edu'; 'kzaterka@rti.org'; 'bkh@rti.org'
Subject: RE: SUPPORT Oximeters

Thank you everyone!!!
Erica Burnell

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 27, 2005 4:56 PM
To: 'wrich@ucsd.edu'; Burnell, Erica
Cc: 'nfiner@ucsd.edu'; 'kzaterka@rti.org'; 'bkh@rti.org'
Subject: Re: SUPPORT Oximeters

Wade
Thanks so much, please get the serial numbers to Betty or Kris.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wade Rich <wrich@ucsd.edu>
To: 'Burnell, Erica' <Erica_Burnell@URMC.Rochester.edu>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
CC: 'Neil Finer' <nfiner@ucsd.edu>
Sent: Tue Sep 27 16:51:42 2005
Subject: FW: SUPPORT Oximeters

Erica,

Yes. Two blue oximeters will go out today if I hurry. If not, early tomorrow am.
Is the address below appropriate for shipping?

Wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 27, 2005 1:47 PM
To: 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'
Subject: Fw: SUPPORT Oximeters

Wade or neil, do you have blue oximeters?? If so, can you let Erica know you can ship them?
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Burnell, Erica <Erica_Burnell@URMC.Rochester.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Tue Sep 27 16:38:14 2005
Subject: Re: SUPPORT Oximeters

Hi Dr. Higgins,
We have a little dilemma here. We have enrolled another SUPPORT baby today and the baby randomized to the blue arm of the Oximeter portion of the study. This happens to be our last blue oximeter. We have placed an order for another set of oximeters, but that may be some time before it is finalized and arrives here. In the mean time we are in need of at least one blue oximeter and preferably two. I am not sure who I should be contacting to possibly have a couple over-night shipped to us. Linda Reubens is out sick today and I know we contacted you the last time we had an issue with the oximeters. Can you help me with this?

Thank you,

Erica Burnell
Golisano Children's Hospital
University of Rochester
Division of Neonatology
Clinical Research Office 4-3251
601Elmwood Ave. Box 651
Rochester, NY 14642

585-275-5427

From: Newman, Jamie
To: Stevens, Timothy
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT Follow-up MOO-First Draft
Date: Tuesday, September 27, 2005 12:57:00 PM
Attachments: SUPPORTFUMOOjn9_26.doc

Attached is the Support Follow-up Manual of Operations (MOO) that I have drafted. This document was created by using the SUPPORT Trial Manual as a template and updating it with information from the SUPPORT Follow-up Protocol. Therefore, there may be sections that we want to delete and other sections to elaborate upon or add. Highlighted in yellow are areas of uncertainty. This document has not been formatted so please do not spend time formatting the document, RTI has administrative support people that can help with this (including updating the table of contents). However, I did not want formatting to delay in getting you something to work with since it is the first draft.

Here are some items that still need to be addressed:
-Add question by question definitions when the forms are forms are deemed nearly final
-Confirm subcommittee names—Will there be a specific SUPPORT FU subcommittee or will the SUPPORT subcommittee or FU PIs oversee the study?
-We will want to be consistent and use either "follow-up" or "follow-on" throughout the documents
-I will confirm that all of the acronyms in the list in Appendix A appear in the text
-I'd like to include Figure 1 on page 9 of the Protocol in the MOO (maybe Section 5.1) because it describes the study well. However, I had problems getting it into the document.
-I'd like to go back through my notes from the specifics of the SC meeting to make sure I didn't miss anything.

Please let me know areas/sections that need additional information.

Thanks, Jamie

Jamie E. Newman, MPH
Statistics Research Division
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

SUPPORT Trial Follow-up Study of Pulmonary Outcomes

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial)

NICHD Neonatal Research Network

Manual of Operations

September 27, 2005

TABLE OF CONTENTS Needs to be updated

Chapter 1

Overview and Trial Design

1.1 Introduction

This manual provides detailed instructions of study procedures for the Follow-up Study of the NICHD SUPPORT Trial Follow-up Study (The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants). This manual should be used as a reference guide for study staff including investigators, coordinators, technicians, and data managers. The trial objectives and design are summarized briefly below. For further discussion to the study background and design, please refer to the Follow-up Study Protocol.

1.2 Study Design

This study is a longitudinal follow-up of surviving infants enrolled, randomized and treated as part of the SUPPORT Trial, which was a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This follow-up study will determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the incidence of symptomatic airway dysfunction and volume of outpatient care in the first 18-22 months corrected age (CA). The individual factors to be tested in this follow-up study are:

1) Symptomatic airway dysfunction and need for outpatient pulmonary care in the first 18-22 months among infants managed with a lower SpO2 range (85% to 89%) as compared to a higher, more conventional SpO2 range (91% to 95%).
2) Symptomatic airway dysfunction and need for outpatient pulmonary care in the first 18-22 months corrected age among infants managed with CPAP and a permissive ventilatory strategy versus infants managed with prophylactic surfactant and conventional ventilation begun in the delivery room and continuing in the NICU.

Table 1 below describes the the study treatment groups. Refer to the SUPPORT Trial Protocol for further details regarding the projected outcomes relative to the study interventions

Table 1: SUPPORT Trial Study Treatment Groups

Randomized Intervention	**Low SpO2 85% to 89%**	**High SpO2 91 to 95%**
Treatment **Early CPAP**	Early CPAP + Low SpO2	Early CPAP + High SpO2

Control **Prophylactic/Early Surfactant**	Control + Low SpO2	Control + High SpO2

1.4 Primary Hypotheses

1) We hypothesize that that relative to infants managed with a higher SpO2 range (91% to 95%), infants managed with a lower SpO2 range (85% to 89%) will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care at 18-22 months' CA.

2) We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

1.5 Secondary Hypotheses

1) We hypothesize that **among infants with CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

2) We hypothesize that **among infants without CLD**, infants managed with early use of CPAP and permissive ventilator strategy relative to infants managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

1.6 Summary of Data Forms

The following is a summary of the data forms used in this study. Further details on each form are provided in subsequent chapters. A complete set of forms can be found in Appendix A.

NICU Discharge-Baseline Interview (SUPF01)
This interview will be administered to the parent or guardian by a trained study nurse prior to NICU discharge. Questions concerning family medical history, anticipated living arrangements, and alternate contact information will be asked.

6 Month and 12 Month Interview (SUPF02)
This interview will be administered to the parent or guardian by a trained telephone interviewer at 6 months' CA and again at 12 months' CA.

18-22 Month Interview (SUPF03)

This interview will be administered to the parent or guardian by a trained telephone interviewer at 18-22 months CA. Questions have been added to the 6 month interview concerning the child's allergies.

Chapter 2

Administration

2.1 Organizational Structure

The NICHD Neonatal Research Network is conducting this study. The Network is funded by the NICHD under cooperative agreements with seventeen institutions comprised of sixteen clinical centers and a data coordinating center. The Steering Committee for the Network consists of the Principal Investigator from each clinical center, the data center, and the NICHD project officer. The Steering Committee Chairman is appointed by NICHD and is not a Principal Investigator from any of the Clinical Centers.

2.2 SUPPORT Trial Follow-up Subcommittee ??Check to confirm??

Will there be a SUPPORT Trial Follow-up Subcommittee? This is what was included in the SUPPORT MOO:
The SUPPORT Protocol Subcommittee is responsible for the preparation and maintenance of the protocol, data forms, and manual of operations. This subcommittee will monitor the overall study performance (including protocol compliance) and will report the progress of the trial to the Steering Committee. SUPPORT Subcommittee members are:

Neil Finer, MD

Waldemar A. Carlo, MD,

Edward F. Donovan MD

Michele Walsh, MD

Shahnaz Duara, MD

Rosemary D. Higgins, MD

Abhik Das, PhD

Ruth Everett, RN

Wade Rich, RRT

I see on the cover page of the SUPPORT Follow-up Protocol that the following names are listed. Drs. Stevens and Szilagyi are not mentioned in the SUPPORT MOO so this will need to updated for the Follow-up Study.
Timothy P. Stevens, MD, MPH
Peter Szilagyi, MD, MPH
Dale Phelps, MD

2.3 Participating NICHD Neonatal Research Network Centers

Centers from the NICHD Neonatal Research Network participating in the trial are listed below. The NICHD center number is indicated in parentheses next to the name of each center and the Neonatal Research Network principal investigator is located in the second column. **Should we add another column for the SUPPORT Follow-up PI? Will there be Follow-up PIs for SUPPORT or will the NRN Follow-up PI's monitor this study? Confirm names**

PARTICIPATING CENTERS	NRN PI	SUPPORT STUDY PI
Case Western Reserve Univ. (3) Rainbow Babies and Children's Hospital	Michele Walsh, MD	Michele Walsh, MD
University of Texas-Dallas (4)	Charles Rosenfeld, MD	Walid Salhab, MD
Wayne State University (5) Children's Hospital of Michigan	Seetha Shankaran, MD	Seetha Shankaran, MD
University of Miami (8) Jackson Memorial Hospital	Shahnaz Duara, MD	Shahnaz Duara, MD
Emory University (9) Grady Memorial Hospital	Barbara J. Stoll, MD	Susie Buchter, MD
University of Cincinnati (11) University of Cincinnati Hospital	Edward F. Donovan, MD	Vivek Narendran, MD Kurt Schibler, MD
Indiana University (12)	James A. Lemons, MD	Brenda Poindexter, MD
Yale University (13) The Children's Hospital at Yale – New Haven	Richard A. Ehrenkranz, MD	Vineet Bhandari, MD
Brown University (14) Women and Infant's Hospital	William Oh, MD	Abbot Laptook, MD
Stanford University (15) Stanford University Med Center	David K. Stevenson, MD	Krisa Van Meurs, MD
University of Alabama (16) University of Alabama at Birmingham	Waldemar A. Carlo, MD	Waldemar A. Carlo, MD
University of Texas- Houston (18)	Jon E. Tyson, MD	Brenda Morris, MD
Duke University (19)	Ronald Goldberg, MD	C. Michael Cotten, MD
Wake Forest University (20)	Michael O'Shea, MD	Michael O'Shea, MD
Golisano Children's Hospital at Strong (21) University of Rochester	Dale L. Phelps, MD	Nirupama Laroia, MD
University of California-San Diego (22)	Neil Finer, MD	Neil Finer, MD

2.3 Responsibilities of the Clinical Centers

The minimum staff required for network participation at each clinical center is the physician Principal Investigator (PI), the Research Coordinator, **and telephone interviewers, if interviews are not conducted by the Research Coordinator.** [redacted] The responsibilities of these individuals are described briefly in this chapter and in more detail in subsequent chapters.

The PI or designee is responsible for ensuring the proper conduct of the trial at his or her clinical center (including recruitment and treatment of patients as specified in the protocol), accurate collection of data and transmission of information to the Data Coordinating Center (DCC). Other specific duties include the following:

- Presenting an in-service to the other physicians
- Applying for IRB approval
- Introducing the study to the parents of prospective patients, and obtaining signed informed consent from the parents of eligible infants (in some centers this responsibility may be delegated)
- Reviewing all infants for whom informed consent has been obtained to confirm their eligibility
- Informing the IRB of the study progress.

The Research Coordinator will be responsible for the day-to-day operations of the study at the clinical center, including data collection and management. This responsibility includes the following:

- Collecting information necessary to complete the data collection forms, and coordinating data entry
- Training and certifying the staff in the use of the network computer
- Controlling access to the network computer and ensuring that required back-up, security and confidentiality are maintained
- Responding to edit messages and other communications from the data center
- Distributing updates of the protocol and of the manual of operations to clinical center staff
- To facilitate patient tracking, Network Centers choosing Rochester to administer questionnaires to their patients (Option 2) will provide contact information to the Rochester site.

2.4 Responsibilities of the University of Rochester Health Services Research Group

Clinical Centers will have the option of administering the follow-up questionnaires to their own patients (Option 1) or having telephone interviewers of the University of Rochester Health Services Research Group administer the follow-up questionnaires to their patients (Option 2). Regardless of the option chosen, each local center will be responsible for obtaining informed consent, administering the discharge questionnaire, and tracking patients following discharge.

In efforts to standardize the administration of the interviews, the University of Rochester Health Services Research Group will be responsible for a program to train interviewers at various centers. To standardize administration of the interview, a program to train interviewers will be undertaken. The program will consist of two parts. Part 1 consists of creation of a videotaped, structured interview in which the Rochester Trainer interviews a simulated patient. The training video will then be distributed and viewed by interviewers at each center. Part 2 will consist of a practice interview in which interviewers from each center interview the Rochester trainer, who simulates a standardized patient. Following the practice interview, the Rochester trainer and practice interviewer will discuss the interview and give feedback. Other responsibilities include:

- Development and distribution of an audio clip of wheezing to be presented along with a verbal definition to the interview respondent to standardize interpretation of wheezing and to minimize ascertainment biases due to language, culture, literacy or interviewing techniques.
- Maintaining trained Spanish-speaking individuals to conduct the telephone interviews with Spanish-speaking participants from centers choosing Rochester to administer the questionnaire to their patients (Option 2).
- Spanish language versions of the questionnaires will be created and made available to all centers. The Cornell Translation Service, a University based professional translation service, will be contracted by the University of Rochester to perform the translation.

2.5 Responsibilities of the Data Coordinating Center

The DCC at RTI International is responsible for all aspects of statistical design and analysis as well as data management of the study. In particular, this includes:

- Processing, updating and distributing the protocol and manual of operations
- Developing and distributing the data forms, including periodic updates as necessary
- Developing, testing and implementing the database and other software. Ensuring that data are correct and complete by implementing editing and auditing procedures
- Monitoring the progress and quality of the study
- Preparing interim and final analyses and reports
- Participating in the preparation of presentations and publications relating to the study

The DCC is also responsible for sending monthly reminder reports to Network Centers. ***Check with RTI Research Computing Division to confirm the following:*** For each enrolled patient, the report will include the following:

- Network number
- Gestational age
- Gender
- Date of last interview
- Answer to question 1 (care taker providing the previous interview)
- Answer to 1a (was interview conducted face to face or by telephone)
- List which of the 4 interviews have been completed (CA = corrected age)
- Completed interviews, date of last interview and answers to question 1 and 1a may be presented as outlined in the table below.

Example table

Required Interviews	Date	Caretaker Interviewed	Face to Face?
▪ Discharge	__/__/__	_____	Y or N
▪ 6 month CA	__/__/__	_____	Y or N
▪ 12 month CA	__/__/__	_____	Y or N
▪ 18-22 month CA	__/__/__	_____	Y or N

- Target date for the current interview with windows within which interview should be accomplished, goal window (target date ± 2 weeks) and acceptable window (target date ± 4 weeks)
- A "postcard date", 5 weeks prior to the contact, when a postcard might be sent to the family reminding them of the upcoming call or visit

2.5 Responsibilities of NICHD

In addition to its role as a funding agency, the NICHD participates in the activities of the cooperative agreement by being represented on the Steering Committee. The Program Official also participates in the development of protocol and in assisting the Steering Committee in the coordination of the studies conducted by the Network. The NICHD Program Official, in conjunction with the RTI Principal Investigator is responsible for monitoring site performance of all participating centers. The Program Official has the following responsibilities:

- Assistance in the development of the study protocol.
- Assistance in the development of capitation-based budgets, including the identification of study costs and special institutional needs.
- Allocation of network resources to meet study needs.
- Facilitation of training meetings, site visits, and subcommittee meetings.
- Participating in preparation of publications.

Chapter 3

Screening, Eligibility, Consent

3.1 Study Population

This follow-up study will include all surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial, which were inborn infants of 24 0/7ths to 27 6/7th weeks at birth for which a decision was made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) were enrolled.

3.2 Inclusion Criteria

- Full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Parents/legal guardians have provided consent for enrollment
- No known major congenital malformations
- Survival to hospital discharge

3.3 Exclusion Criteria

- Transport to the center after delivery
- Research apparatus/study personnel are not available.

3.4 Informed Consent

Every effort will be taken to enroll ALL SUPPORT Trial patients into the Follow-up Study, including currently enrolled SUPPORT patients (both patients still in NICU and those discharged) and future enrollees. By obtaining pulmonary outcome data for both current and future SUPPORT patients, death or adverse pulmonary outcome can be analyzed as competing outcomes. Each local center will be responsible for obtaining informed consent for the Follow-up Study regardless of whether they are administering the follow-up questionnaires to their patients or Rochester is conducting the telephone interviews.

For future enrollees in the SUPPORT Trial, consent for the Follow-up study will be obtained at the time of enrollment in the main trial. As described in the SUPPORT Trial Manual of Operations, these infants will be recruited for the study by approaching one or both parents at the time of admission to the hospital at risk for premature delivery at 27 weeks or less. It is anticipated that, whenever possible, the parents will be approached by study personnel to discuss the trial and obtain an informed consent for the participation of the infant at delivery. Randomization will be by family, thus all offspring will be randomized to the same trial arms, provided adequate equipment and personnel are available at the time of delivery. Sample consent forms for currently enrolled and future SUPPORT patients are attached (Appendix C).

3.5 Screening Procedures

This follow-up study will include all surviving infants enrolled, randomized and treated as part of the NICHD Neonatal Research Network SUPPORT Trial.

For future enrollees in the SUPPORT Trial, all admissions for threatened premature delivery will be screened on a daily basis to ensure that eligible patients can be enrolled. Obstetrical colleagues at each participating institution will be informed of the nature of this study and encouraged to discuss this study with their patients at risk of premature delivery. The study coordinator at each site will maintain a screening log of potentially eligible patients. In addition, the usual practice of neonatal consultation for all such at risk deliveries will provide a second opportunity to approach mothers with fetuses at risk of preterm delivery.

Chapter 4

Randomization

4.1 Randomization Procedures

Randomization for the NICHD Neonatal Research Network SUPPORT Trial was stratified by gestational age group (24 - 25 6/7 and 26 - 27 6/7) and occurred prior to delivery for consented deliveries. The randomizations were performed by utilizing specially prepared envelopes. The Data Center prepared brown sealed envelopes which contained the identity of the treatment combination that were assigned to the infants enrolled into the study. Deliveries were randomized as a unit, thus multiples, twins, triplets etc were randomized to the same arm of the trial. One envelope corresponded to the delivery of a consenting mother regardless of the number of babies delivered so that all babies from a given delivery received the same treatment combination.

Refer to Section 4.1.1 of the NICHD Neonatal Research Network SUPPORT Trial Manual of Operations (MOO) for more information on randomization and masking as well as storing and assigning oximeters that occurred during the main study.

During the Follow-up Study activities, research coordinators and telephone interviewers, if different from the research coordinators, will remain blinded as to whether infants were randomized to the control or treatment group.

Chapter 5

Follow-up Study Procedures

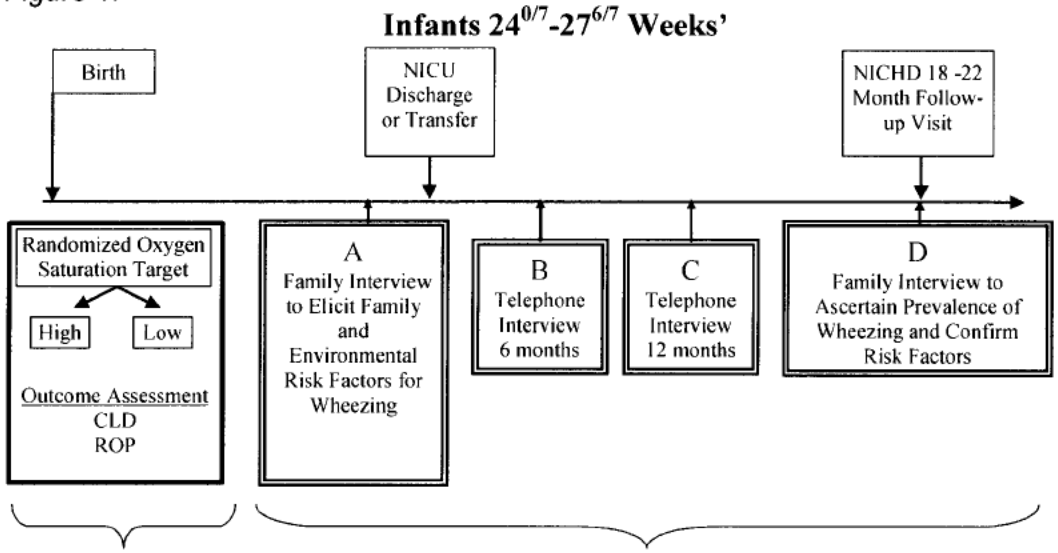
5.1 Study Interventions

Refer to Chapter 5 of SUPPORT Trial Manual of Operations (MOO) for more information on the study interventions and the procedures for the treatment groups. The same questionnaires will be administered to both treatment groups in the Follow-up Study.

Before delivery, infants will be randomized to subsequent management with high vs. low target oxygen saturation according to the SUPPORT Protocol. The SUPPORT Follow-on Study of Pulmonary Outcomes begins just prior to NICU discharge. See Figure 1 for a diagram of the SUPPORT Trial

SUPPORT Trial Follow-on Study

Figure 1.



Follow-up Study procedures. **(Insert Figure 1 of SUPPORT Follow-up Protocol here).**

5.2 Administration of the Follow-up Questionnaires

The target date for conducting the interviews is ± 2 weeks, however, the acceptable window for conducting the interviews is ± 4 weeks.

Clinical Centers have the option of administering the follow-up questionnaires to their own patients (Option 1) or having telephone interviewers of the University of Rochester Health Services Research Group administer the follow-up questionnaires to their patients (Option 2). Table 2 indicates which option the centers have chosen.

	Local Center	Local Center	Rochester
Consent	✓	✓	
Questionnaire at Discharge	✓	✓	
Patient Tracking	✓	✓	
Questionnaire at 6 & 12 mo.	✓		✓
Questionnaire at 18-22 mo.	✓		✓
Data Entry (questionnaires)	✓		✓

Table 2. **SUPPORT Trial - Pulmonary Outcomes Study**

6, 12 and 18-22 Month Pulmonary Questionnaires

NICHD Site	*Administered By*	*Option Number*
Alabama	Alabama	1
Brown	Brown	1
Cincinnati	Cincinnati	1
CWRU	CWRU	1
Dallas	Dallas	1
Duke	Duke	1
Emory	Rochester	2
Houston	Rochester	2
Indiana	Rochester	2
Miami	Miami	1
Rochester	Rochester	2
Stanford	Rochester	2
UCSD	UCSD	1
Wake Forest	Wake Forest	1
Wayne State	Wayne State	1
Yale	Yale	1

Regardless of the option chosen, each local center is responsible for obtaining informed consent, administering the NICU Discharge-Baseline Interview (SUPF01), and tracking patients following discharge. Table 3 further describes the responsibilities of the local center and Rochester in Option 1 and Option 2. **Reformat and insert Figure 2 from Protocol as Table 3 here.**

5.2 Protocol Violations

The occurrence of any one of the following criteria will determine whether an individual infant will be considered a protocol violation:

1. **Are there protocol violations expected in the FU study? i.e., Starting the interview within the FU window but completing it after the window has expired**

All protocol violations will be reviewed by the center PI who will discuss each protocol violation with the involved clinicians [redacted]

[redacted]

5.3 Adverse Events

Serious and unanticipated adverse events were anticipated in the main study for this vulnerable population. Data on potential adverse events that could have potentially been related to the study maneuver were recorded and evaluated as part of continuous safety monitoring during the trial by RTI. Refer to Section 5.5 of the NICHD Neonatal Research Network SUPPORT Trial MOO for more information on adverse event reporting and monitoring.

Will any adverse events noted (i.e. death of child since last contact) during the interviews need to be reported or recorded as AE's? If yes, will RTI need to continue monitoring AE's in terms of treatment groups in the FU as was done in the main study?

Chapter 7

NICU Discharge-Baseline Interview

7.1 Instructions for completing the NICU Discharge-Baseline Interview (SUPF01)

This interview should be administered to the parent/guardian by a trained study nurse prior to NICU discharge.

Heading- Infant's Identification

The following information is included in the heading section of all patient specific data forms: Center, Site, Network Number, Birth Number and Mother's Initials **(optional). Confirm header information**

Chapter 8

6 and 12 Month Pulmonary Outcome Questionnaires

The same questionnaire will be administered by telephone to the child's parent or guardian at 6 and 12 months' CA to assess pulmonary outcomes. These interviews will be administered to the parent or guardian by a trained telephone interviewer at 6 and 12 months' CA.

The interviewer should advise the parent or guardian to call his/her child's doctor if concern about a health issue is raised during the interview.

8.1 Instructions for completing the 6 Month and 12 Month (SUPF02) Pulmonary Outcome Questionnaires Needs to be Updated

Chapter 9

18-22 Month Questionnaire

This questionnaire will be administered by telephone to the child's parent or guardian at 18-22 months CA to assess pulmonary outcomes.

The interviewer should advise the parent or guardian to call his/her child's doctor if concern about a health issue is raised during the interview.

Update the following sections

9.1 Instructions for completing the 18-22 Month Questionnaire (SUPF03)

APPENDIX A

List of Acronyms

BOOST Trial – Benefits of Oxygen Saturation Targeting
BPD – Bronchopulmonary Dysplasia
CA – Corrected Age
CLD – Chronic Lung Disease
CPAP – Positive pressure applied with a face mask to help keep lungs inflated
FEF – Forced Expiratory Flow
GA – Gestational Age
GDB – Generic Data Base for the NICHD Neonatal Research Network
HDMA – House Dust Mite Allergen
HIPPA – Health Insurance Portability and Accountability Act of 1996
HSR Group – University of Rochester Health Services Research Group
IRB – Institutional Review Board
LBW – Low Birth Weight
NBW – Normal Birth Weight
NHLBI Consensus Expert Report -
NICHD – The National Institute of Child Health and Human Development
NICU – Neonatal Intensive Care Unit
PFT – Pulmonary Function Testing
RDS – Respiratory Distress Syndrome
ROP – Retinopathy of Prematurity
RSV - Respiratory Syncytial Virus
SP02 –
SUPPORT Trial– The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants
UKOS – The United Kingdom Oscillator Study
VLBW – Very Low Birth Weight

APPENDIX B

FOLLOW-UP STUDY FORMS

SUPF01 **NICU Discharge-Baseline Interview**

SUPF02 **6 Month Interview and 12 Month Interview**

SUPF03 **18-22 Month Interview**

Insert Forms

APPENDIX C

SAMPLE CONSENT FORMS

Insert

From: Brenda Poindexter
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Lemons, James A
Subject: Re: SUPPORT GROWTH SECONDARY
Date: Monday, September 26, 2005 1:08:16 PM

Rose,
Indiana votes for #1. We will put this through as an amendment to SUPPORT for the additional data collection so that we don't need an additional consent form (like Neil, we will have a separate consent for the MRI secondary).
Brenda

HI,
I need a vote from the PI's regarding the SUPPORT GROWTH SECONDARY presented by Dr. Duara last week at the steering committee meeting.

Please indicate your preference:

1. Yes – this needs to go forward without additional funding and should start now
2. Yes – this needs to go forward and we should commit funds from the 2006 budget (this will impact the possibility of other protocols being instituted)
3. No – this needs to wait for the next budget period with reassessment in April 2006
4. No – this should not be done

I have attached the protocol.
Send me your vote by September 30.

Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]; bpoindex@iupui.edu; michele.walsh@case.edu; adas@rti.org; bkh@rti.org; jlemons@iupui.edu; lucmille@iupui.edu
Cc: "Neil Finer"
Subject: RE: Physiologic Definition
Date: Thursday, September 22, 2005 5:00:36 PM

The PHY forms are not approved for any research protocols in my institution except for SUPPORT. PD is no longer an approved protocol. I can not reference an amendment to the GDB protocol saying we will collect this form if the protocol amendment itself does not exist. I do not see how we could get approval to send the data to RTI until the GDB protocol containing a reference to the PHY forms is finalized.
Wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, September 22, 2005 1:33 PM
To: 'bpoindex@iupui.edu'; 'michele.walsh@case.edu'; 'wrich@ucsd.edu'; 'adas@rti.org'; 'bkh@rti.org'; 'jlemons@iupui.edu'; 'lucmille@iupui.edu'
Subject: Re: Physiologic Definition

If the physiologic definition data are collected as part of an approved protocol (I.e. Support), then they can be transmitted to rti. If these data are collected as part of GDB, the Approval must be requested as an ammendment to GDB UNTIL WE HAVE THE NEW PROTOCL READY FOR DISSEMINATION IF the data are transmitted to rti.

Thanks
Rose.

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Brenda Poindexter <bpoindex@iupui.edu>
To: Michele Walsh <michele.walsh@case.edu>; wrich@ucsd.edu <wrich@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; Abhik Das <adas@rti.org>; Hastings, Betty J. <bkh@rti.org>; Lemons, James A <jlemons@iupui.edu>; Miller, Lucy C. <lucmille@iupui.edu>
Sent: Thu Sep 22 16:09:44 2005
Subject: Re: Physiologic Definition

We have been transmitting data related to the physiologic definition (on babies enrolled in SUPPORT and on babies not in SUPPORT) to RTI. Lucy has told me that this is on a separate data form. If this is not a part of GDB, then we do not have IRB approval to be sending this data. We should either have all sites make an immediate amendment to GDB to include the physiologic definition - or should wait to send any data related to the physiologic definition on non-SUPPORT babies until after the revised GDB is approved by our IRBs. We should be okay on babies enrolled in the SUPPORT trial because the physiologic definition is mentioned in the protocol. Please advise how you want us to proceed - it sounds like many sites have the same concern.
Thanks, Brenda

> Hi All: It is my understanding that we incorporated the Phys DEf as
> part of the GDB.
> I updated the manual to reflect that it is a component of the GDB.
> Of course this is the new version that is intended for implementation
> in 06.
> Regards, Michele
>
> ----- Original Message -----
> From: Wade Rich <wrich@ucsd.edu>
> Date: Wednesday, September 21, 2005 4:30 pm
> Subject: RE: Physiologic Definition
>> I think the point is, that until the GDB mentions the physiologic
>> definitionspecifically, none of us have a waiver to use the data.
>> Once it becomes
>> part of the new forms, assuming that occurs, we will be able to
>> provide the data under waiver. According to Nancy N. it has still
>> yet to be worked out exactly how the GDB will incorporate the PD.
>> wade
>>

>>
>> We also have a waiver for GDB.
>>
>> Charles
>>
>>
>>
>> Charles R. Rosenfeld, M.D.
>> George L. MacGregor Professor of Pediatrics
>> and Professor of Obstetrics and Gynecology Director, Division of
>> Neonatal-Perinatal Medicine UT Southwestern Medical Center at Dallas
>> 5323 Harry Hines Blvd.
>> Dallas, TX 75390-9063
>> Telephone: (214) 648-3903
>> FAX: (214) 648-2481
>> Email: charles.rosenfeld@utsouthwestern.edu
>>
>>>>> Richard Ehrenkranz <richard.ehrenkranz@yale.edu> 09/21/05 4:02
>> PM
>>>>>>>>
>> Rose:
>> We instituted this as standard of care several years ago, and as far
>> as I am concerned, this is no different than GDB for which we have a
>> waiver of consent.
>> Richard
>>
>> At 05:43 PM 9/20/2005, Higgins, Rosemary (NIH/NICHD) wrote:
>>> Hi,
>>> An IRB question for the physiologic definition of BPD has come up
>>> regarding transmission of data to RTI. If the physiologic
>> definition
>>> has been instituted as "standard care at your site," the IRB
>> still
>>> needs to give you permission to collect the data for research
>> purposes.

>>> They may not require parental consent, but data that are
>> collected for
>>> research purposes must have IRB approval (usually waiver of
>> consent) to
>>> be transmitted to the data center. Let me know if there are
>> questions
>>> or concerns about this particular item.
>>>
>>> Thanks
>>> Rose
>>>
>>> Rosemary D. Higgins, M.D.
>>> Program Scientist for the Neonatal Research Network Pregnancy and
>>> Perinatology Branch Center for Developmental Biology and
>> Perinatal
>>> Medicine NICHD, NIH 6100 Executive Blvd., Room 4B03B MSC 7510
>> Bethesda,
>>> MD 20892 (For overnight delivery, use Rockville, MD 20852)
>>> 301-435-7909
>>> 301-496-3790 (FAX)
>>> <mailto:higginsr@mail.nih.gov>higginsr@mail.nih.gov
>>>
>>
>> Richard A. Ehrenkranz, MD
>> Department of Pediatrics
>> Yale University School of Medicine
>> 333 Cedar Street
>> PO Box 208064
>> New Haven, CT 06520-8064
>> tele: 203-688-2320
>> fax: 203-688-5426
>>
>> The information contained in this email may be privileged and
>> confidential.If you are the intended recipient, you must maintain
>> this message in a secure and confidential manner. If you are not the
>> intended recipient, please notify the sender immediately and destroy
>> this message.
>> Thank you.
>>
>>
>>

From: Nancy Peters
To: Neil Finer; wrich@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; bkh@rti.org; Michael O`Shea; Robert Dillard
Subject: SUPPORT, high flow NC, etc
Date: Thursday, September 22, 2005 1:36:22 PM

Neil,

I know the subject of high flow nasal cannuals and the SUPPORT Trial has been a topic of discussion for many months. I do find that we seem to have an everchanging definition..... such as (1) in the January 6th e-mail Q&A on SUPPORT, high flow nasal cannula was defined as 1 liter or greater, (2) the coordinators minutes dated April 25th, state that for the purpose of the survey on the use of high flow nasal cannuals---- the definition was 1/2 liter or greater, (3) Tech Memo 2 of May 5th instructs us to use the definiton of >500cc/min to define "support" (room air nasal cannula) for the SUPP11 form, and (4) during discussions at our recent steering committee meeting high flow was defined as 2 liters per minute.

Could we please have a *Tech Memo* (#4) issued that presents the current definition of high flow nasal cannula? This would help to appease our staff, our IRB's and make sure that we all were consistent with the use of that definition in our practices throughout all 16 centers (and the definition of high flow NC varies from site to site------Would also help us to know if we have to complete a study deviation form). **In addition, it would be helpful if you included a statement about disabling the high alarm on the study oximeter when the infant is on room air and it is constantly alarming (our recent experience and your instructions** -------same reasons -- makes staff and IRB's feel comfortable that we are following study protocol).

I do need some clarification of the use of NC/hood, (Form SUPP05). The instructions are: "Complete section B if infant is on cannual/hood for > 8 hours on this day". Is that 8 hours total use in a day, or NC/hood used for an 8 hour time period? Our study infant received 400cc NC for 3 hours yesterday as the nares were pink....but no skin breakdown. If there is a temporary switch to NC or hood to help preserve skin integrity...do we only answer that question if it is for 8 consecutive hours or for 8 cumulative hours? (Infant continues to do well and has had an occasional oxygen requirement to 30%, but remains primarily on RA. This has been great for acceptance of the study as it has provided a positive response to using early CPAP in these small infants.)

At our center we may on occasion transfer an infant from site 1 to site 2 (census reasons, requirement for PDA ligation, ROP surgery, and that nemesis NEC). We cannot transport the oximeter with the infant as each hospital requires that their own bio-med people do the electrical check on the unit before it can be used. There may be some times that we may not have an oximeter at Site 2 and have to borrow one and wait for a check before it can be put into use. What is the time period allowed for the infant to be off of a study oximeter before we compete a protocol deviation" Two hours ....like the protocol for initial admission to the nursery? This would also apply to those infants that come off of oxygen, have their oximeter discontinued after 72 hours, go back on oxygen....and require a study oximeter because they have not reached the 36 wks date. **We need a statement about time between going back on oxygen and application of study oximeter before protocol deviation** --- ***plus a definitive statement of how many hours in a 24 hour clock on oxygen before study oximeter must be replaced on infant (four hours of oxygen therapy?, eight hours?, 12 hours?) needs to be included in a Tech Memo.***

Thank you for making yourself available to answer our questions. Many of these things we discuss in meetings and on conference calls. It would be so helpful if they could then be summarized and sent to us as a Tech Memo or FAQ update so that we can have clear guidelines to put into practice.

Nancy P.

From: Richard Ehrenkranz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT GROWTH SECONDARY
Date: Thursday, September 22, 2005 1:13:40 PM

Rose:
I vote Yes and think that this should go forward without additional funding and should start now.
Richard

At 04:25 PM 9/20/2005, you wrote:

> HI,
> I need a vote from the PI's regarding the SUPPORT GROWTH SECONDARY presented by Dr. Duara last week at the steering committee meeting.
>
> Please indicate your preference:
>
> 1. Yes – this needs to go forward without additional funding and should start now
> 2. Yes – this needs to go forward and we should commit funds from the 2006 budget (this will impact the possibility of other protocols being instituted)
> 3. No – this needs to wait for the next budget period with reassessment in April 2006
> 4. No – this should not be done
>
> I have attached the protocol.
> Send me your vote by September 30.
>
> Thanks
> Rose
>
> Rosemary D. Higgins, M.D.
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine
> NICHD, NIH
> 6100 Executive Blvd., Room 4B03B
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> 301-435-7909
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

From: Gratton, Teresa (grattotl)
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support Trial - Follow-Up
Date: Thursday, September 22, 2005 1:07:00 PM

Hi Rose – I wanted to change our participation in the Support Trial re: the Supplemental Respiratory Questionnaire. We would like to do Option 1. It will be easier for us to consent and track in Cincinnati if we do all the tracking aspects. Do I need to do anything further than contact you? Thanks, Tari Gratton

From: Abbot Laptook
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Angelita Hensman
Subject: RE: SUPPORT GROWTH SECONDARY
Date: Thursday, September 22, 2005 9:08:46 AM

Rose
I would go forward with it presently (ie choice number 1) but would want to see the issues raised at the steering committee properly addressed. Abbot

---

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 21, 2005 4:46 PM
To: Abbot Laptook
Cc: Angelita Hensman
Subject: RE: SUPPORT GROWTH SECONDARY

Abbot
The vote for the growth secondary is "as is" but suggestions can be passed along. For the SUPPORT pulmonary secondary study, there was a brief survey at discharge which I thought was included with prior versions – up to the sites who does it.

Thanks
Rose

From: Abbot Laptook [mailto:ALaptook@WIHRI.org]
Sent: Wednesday, September 21, 2005 10:44 AM
To: Higgins, Rosemary (NIH/NICHD)
Cc: Angelita Hensman
Subject: RE: SUPPORT GROWTH SECONDARY

Rose
I heard a number of concerns regarding this protocol that I think need to be addressed. Specifically there is the concern about the safety of doing length measurements on fragile infants during the first few weeks of life when their respiratory status is tenous. The other issue is the frequency of the measurements and whether we really need weekly meaurement of head and length during the first month of life. Will this be clarified or are we voting for the protocol as is?
A second unrelated issue is the pulmonary survey for the support trial. Previous versions started with surveys at 6 months as I recall but I now see that the recent version is expected to start prior to discharge. I guess I missed when this happens but was this discussed or mentioned? I don't recall hearing about it. It does impact who will be doing the initial survey ie coordinator or follow-up personnel. We were viewing this as something that could totally be done as part of follow-up when the mother comes in. Can you bring me up to speed on this one? Tx, AL

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 20, 2005 4:25 PM
To: Abbot Laptook; Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: Petrie, Carolyn
Subject: SUPPORT GROWTH SECONDARY

HI,

I need a vote from the PI's regarding the SUPPORT GROWTH SECONDARY presented by Dr. Duara last week at the steering committee meeting.

Please indicate your preference:

1. Yes – this needs to go forward without additional funding and should start now
2. Yes – this needs to go forward and we should commit funds from the 2006 budget (this will impact the possibility of other protocols being instituted)
3. No – this needs to wait for the next budget period with reassessment in April 2006
4. No – this should not be done

I have attached the protocol.
Send me your vote by September 30.

Thanks
Rose

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

From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT GROWTH SECONDARY
Date: Wednesday, September 21, 2005 5:46:07 PM

Obviously, if I am allowed to vote, I choose # 1.
Shahnaz

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 20, 2005 4:25 PM
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: Petrie, Carolyn
Subject: SUPPORT GROWTH SECONDARY

HI,
I need a vote from the PI's regarding the SUPPORT GROWTH SECONDARY presented by Dr. Duara last week at the steering committee meeting.

Please indicate your preference:

1. Yes – this needs to go forward without additional funding and should start now
2. Yes – this needs to go forward and we should commit funds from the 2006 budget (this will impact the possibility of other protocols being instituted)
3. No – this needs to wait for the next budget period with reassessment in April 2006
4. No – this should not be done

I have attached the protocol.
Send me your vote by September 30.

Thanks
Rose

Rosemary D. Higgins, M.D.
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higginsr@mail.nih.gov

From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT GROWTH SECONDARY
Date: Wednesday, September 21, 2005 12:06:46 PM

Rose
Since SUPPORT has started I vote for 1
Seetha

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 20, 2005 4:25 PM
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: Petrie, Carolyn
Subject: SUPPORT GROWTH SECONDARY

HI,
I need a vote from the PI's regarding the SUPPORT GROWTH SECONDARY presented by Dr. Duara last week at the steering committee meeting.

Please indicate your preference:

1. Yes – this needs to go forward without additional funding and should start now
2. Yes – this needs to go forward and we should commit funds from the 2006 budget (this will impact the possibility of other protocols being instituted)
3. No – this needs to wait for the next budget period with reassessment in April 2006
4. No – this should not be done

I have attached the protocol.
Send me your vote by September 30.

Thanks
Rose

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From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT pilot
Date: Wednesday, September 21, 2005 10:02:01 AM

-----Original Message-----
From: Hastings, Betty J.
Sent: Wed 9/21/2005 9:46 AM
To: Petrie, Carolyn
Subject: RE: SUPPORT pilot

There were only 16 enrolled, from 4 sites. No one has enrolled in this study since May. Wally stated (after I asked) that they were no longer doing this study. I'm not sure why, but that is why Cathy Grisby asked the question.

-----Original Message-----
From: Petrie, Carolyn
Sent: Wednesday, September 21, 2005 9:41 AM
To: Hastings, Betty J.
Subject: FW: SUPPORT pilot

Betty-

from rose.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wed 9/21/2005 9:37 AM
To: Petrie, Carolyn
Subject: Re: SUPPORT pilot

Betty or Kris can look to see how many are enrolled. If there are 200, then I think that was the designated n.

Sent from my BlackBerry Wireless Handheld

From: Michele Walsh
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT GROWTH SECONDARY
Date: Tuesday, September 20, 2005 6:34:44 PM
Attachments: .msg
mcw3.vcf

Option 2.
Michele

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT GROWTH SECONDARY
Date: Tuesday, September 20, 2005 6:18:51 PM

I vote for #1 and suggest to eliminate/reduce some of the frequent measements and reduce the trajectory. Part of the study.
Wally
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
To: Abbot Laptook (alaptook@WIHRI.org) <alaptook@WIHRI.org>; Abhik Das <adas@rti.org>; Brenda Poindexter <bpoindex@iupui.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Charles Rosenfeld <crosen@mednet.swmed.edu>; Dale Phelps <dale_phelps@urmc.rochester.edu>; Ed Donovan <edward.donovan@cchmc.org>; Ehrenkranz Richard (E-mail) <richard.ehrenkranz@yale.edu>; Jobe Alan (E-mail) <Jobea0@chmcc.org>; Lemons Jim (E-mail) <jlemons@iupui.edu>; Michael O'Shea <moshea@wfubmc.edu>; Michelle Walsh <mcw3@po.cwru.edu>; Neil Finer <nfiner@ucsd.edu>; Oh William (E-mail) <william_oh@brown.edu>; Poole Kenneth (E-mail) <poo@rti.org>; Ronald GOldberg <goldb008@mc.duke.edu>; Shahnaz Duara <sduara@miami.edu>; Shankaran Seetha (E-mail) <s_shankaran@wayne.edu>; Stevenson David (E-mail) <dstevenson@stanford.edu>; Stoll Barbara (E-mail) <barbara_stoll@oz.ped.emory.edu>; Tyson Jon (E-mail) <Jon.E.Tyson@uth.tmc.edu>; Walid Salhab (Walid Salhab) <Walid.Salhab@UTsouthwestern.edu>
CC: Petrie, Carolyn <petrie@rti.org>
Sent: Tue Sep 20 15:25:27 2005
Subject: SUPPORT GROWTH SECONDARY

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Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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From: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT GROWTH SECONDARY
Date: Tuesday, September 20, 2005 5:16:18 PM
Attachments: growthprot revised Aug 9 2005.doc

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we vote for #1

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

09/20/2005 04:25 PM

To: "Abbot Laptook (alaptook@WIHRI.org)" <alaptook@WIHRI.org>, Abhik Das <adas@rti.org>, Brenda Poindexter <bpoindex@iupui.edu>, "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>, Charles Rosenfeld <crosen@mednet.swmed.edu>, Dale Phelps <dale_phelps@urmc.rochester.edu>, Ed Donovan <edward.donovan@cchmc.org>, "Ehrenkranz Richard (E-mail)" <richard.ehrenkranz@yale.edu>, "Jobe Alan (E-mail)" <Jobea0@chmcc.org>, "Lemons Jim (E-mail)" <jlemons@iupui.edu>, "Michael O'Shea" <moshea@wfubmc.edu>, Michelle Walsh <mcw3@po.cwru.edu>, Neil Finer <nfiner@ucsd.edu>, "Oh William (E-mail)" <william_oh@brown.edu>, "Poole Kenneth (E-mail)" <poo@rti.org>, Ronald GOldberg <goldb008@mc.duke.edu>, Shahnaz Duara <sduara@miami.edu>, "Shankaran Seetha (E-mail)" <s_shankaran@wayne.edu>, "Stevenson David (E-mail)" <dstevenson@stanford.edu>, "Stoll Barbara (E-mail)" <barbara_stoll@oz.ped.emory.edu>, "Tyson Jon (E-mail)" <Jon.E.Tyson@uth.tmc.edu>, "Walid Salhab (Walid Salhab)" <Walid.Salhab@UTsouthwestern.edu>

cc: "Petrie, Carolyn" <petrie@rti.org>
Subject: SUPPORT GROWTH SECONDARY

HI,
I need a vote from the PI's regarding the SUPPORT GROWTH SECONDARY presented by Dr. Duara last week at the steering committee meeting.

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August 9, 2005

Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study: A Proposed Secondary Study

Cristina Navarrete MD, and Shahnaz Duara MD
University of Miami Miller School of Medicine, Miami, FL.

Abstract:

Post-natal growth restriction is a major problem in preterm infants. Perturbations in oxygenation are recognized to influence post-natal growth; hypoxic conditions can directly impair growth and hyperoxic conditions predispose infants to BPD, which in turn has been linked to poor growth. The NICHD Neonatal Network is conducting a prospective trial of preterm infants randomized to two levels of baseline oxygen saturations. The effect of baseline saturations on pulmonary morbidity and ROP are the primary outcome measures. With respect to post-natal growth, there is a paucity of data relating alterations in baseline oxygen saturation and/or frequent deviations above or below the baseline to growth outcomes. We propose a secondary study to quantify short-term growth velocity in-hospital and long-term growth at 18-22 months of corrected age for infants enrolled in the SUPPORT Trial in relationship to oxygen saturation.

A. Hypothesis to be tested

Primary:

1. Infants in the low oxygen saturation group (85-89%) will have better in-hospital and long-term (18-22 months corrected age) growth.

2. Trajectories of growth in hospital will be better for infants in the low oxygen saturation group.

Secondary:

1. Growth will be greater in infants who spend > 50% of the time with daily median oxygen saturation between 85% -95% while on supplemental oxygen, independent of randomization to low or high oxygen saturation.

2. Infants with BPD will have poorer in-hospital and long-term growth than infants without BPD, independent of the saturation randomization arm.

3. Better long-term growth will be positively related to neuro- developmental outcome, independent of the saturation randomization arm.

B. Specific Aims:

1. To determine anthropometric measurements (wt, HC, length) in infants randomized to low and high oxygen saturation arms, from birth to hospital discharge and again at 18-22 months corrected age.
2. To determine nutritional intake (parenteral and enteral) during hospital stay.
3. To determine the percentage of infants with growth <10 percentile at 36 weeks PMA or discharge, whichever comes first.
4. To determine the percentage of infants with growth <10 percentile at 18-

22 months corrected age.

5. To determine growth in relation to the proportion of time spent with oxygen saturation
    a. <85% and >95%
    b. 85%-95%
6. To determine growth in relation to infants' median oxygen saturation while in supplemental oxygen
    a. median oxygen saturation > 95%
    b. median oxygen saturation 85% - 95%
    c. median oxygen saturation < 85%
7. To relate incidence of BPD in low and high saturation arms to growth.
8. To determine in-hospital growth velocity/trajectory in low and high saturation arms.
9. To determine long-term growth velocity/trajectory, from hospital discharge to follow up at 18-22 months corrected age in low and high saturation arms.
10. To relate neuro-developmental outcome at 18-22 months corrected age to long-term growth in low and high saturation arms.

Rationale:

The SUPPORT Trial will randomize infants to two ranges of SpO2 in order to test the hypothesis that use of a lower SpO2 range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity and/or the need for surgical intervention. Retrospective cohort data from several units in the U.K., with different oxygen supplementation policies, revealed poorer growth patterns in the preterm infants exposed to higher oxygen saturations for the duration of oxygen exposure (Tin 2001). Conversely, observational data of infants with established BPD show better growth with home oxygen support (Groothius 1987), and two recent RCT of different target saturations in older oxygen-dependent premature infants showed no difference in short or long-term growth outcomes (STOP-ROP 2000, BOOST Trial 2003). There are no RCT data evaluating the short or long-term growth impact of different SpO2 strategies with supplemental oxygen use in a birth cohort of extremely preterm infants. Therefore, this study provides an opportunity for us to obtain critically needed growth information on premature infants who are exposed from birth to different target oxygen saturation strategies.

Background

Improvements in antenatal care, respiratory support and nutrition have contributed to increased survival of ELBW infants. As the number of survivors increase, the long term outcome of these infants becomes more important. Lemons et al described growth failure or weight <10th percentile at 36 weeks postmenstrual age in 97% of ELBW infants surviving to discharge. Some morbidities in adulthood are linked to growth during the early post-natal period (Singhal 2004) and make adequacy of growth in this population of heightened interest.

Instead of following intra-uterine growth curves of age matched fetuses, VLBW infants exhibit wide-spread post-natal growth retardation (Cooke 2004), losing ground during the first weeks of life (Berry 1997). To resume growth post-natally, nutrition is of paramount

importance; however, other factors such as severity of illness and perhaps oxygenation also play a role. Observational studies of infants with BPD showed poor post-natal growth when infants were sent home without oxygen supplementation (Markestad 1981).

Although preterm infants without lung disease attain oxygen saturations >95%, artificial attempts to keep arterial oxygenation at a "physiological" level may not be beneficial to growth, the lung or retina (Tin 2001). Animal studies have shown that newborn mammals (mice, rats, guinea pigs) develop poor growth with chronic hypoxia and that blunted body growth is directly proportional to the profundity of the exposure to chronic hypoxia (Mortola 1990). Chronic hypoxemia has also been suggested as the cause of poor growth in patients with cyanotic congenital heart disease (Dundar 2000). When home oxygen supplementation was discontinued inappropriately by parents in a cohort of VLBW infants with BPD, there was a deceleration in the rate of weight gain, which improved when oxygen supplementation was resumed (Groothius 1987). Hudak et al in 1989 observed that ELBW infants with CLD who went home on oxygen supplementation had good catch-up growth at 19 months. Taken collectively, these data suggest that hypoxic conditions affect growth negatively and supplementing oxygen may improve growth.

The optimal level of oxygen saturation to promote post-natal growth is unknown. Most of the available human data is limited to oxygen supplementation of infants who are oxygen dependent or have BPD. Baraldi et al demonstrated that discharged infants with BPD, who were kept on supplemental oxygen to keep saturations above 94%, had progressive but poor weight gain (stayed below 3rd percentile) at 9 months corrected age follow-up. In infants with BPD whose oxygen supplementation was intentionally discontinued, the subset who exhibited episodes of desaturations below 88-91% had a significant decline in the rate of weight gain as compared to those who maintained saturations above 92% (Moyer-Mileur 1996). Conversely, when two different oxygen saturation control policies (high: 88-98% and low: 70-90%) were retrospectively reviewed in <28 week gestation infants, the infants being cared for in the high oxygen saturation policy units were more likely to weigh less than the 3rd percentile at discharge (45% vs. 17%, Tin 2001). The infants assigned to the high oxygen saturation limits were also more likely to have BPD and ROP.

Recently, the BOOST Trial demonstrated that randomizing infants born <30 weeks gestation who were still on oxygen at 32 weeks postmenstrual age either to standard saturations (91-94%) or to high saturations (95-98%) produced no significant difference in growth at 12 months corrected age. This study, while randomizing infants to two different levels of saturations (conventional and high), only enrolled infants if they were still on oxygen supplementation at 32 weeks PMA and used higher limits than planned by SUPPORT. Our proposal is novel in that randomization to the two oxygen strategies begins at birth and continues for as long as the infants are in supplemental oxygen - by implementing this secondary we will be able to determine the impact of these strategies on short and long-term growth.

Methods:

Anthropometric Measures – at birth, postnatal days 7, 14, 21, and 28 days, 32 w PMA and 36 w PMA or discharge (wt, length, HC)

1. Weight - using standard digital electronic scales (c/o infant's nurse)
2. Length - using the Premie Length Board (average of two values, c/o research staff)

3. Head circumference - using paper measurement tape (average of two values c/o research staff)

Clinical Data-

1. Date when infant regains birth weight
2. Date of first enteral feed
3. Date of full enteral feeds (enteral > 120ml/kg/d)
4. Total number of days on parenteral nutrition
5. 24 h intake 'snapshots' (Parenteral, Enteral) – postnatal days 7, 14, 21, and 28, 32w PMA, 36w PMA or discharge (whichever comes first)
6. Presence of BPD

Intervention Data –

1. Duration of time spent in target saturation ranges of interest (Already part of SUPPORT‡)
2. Median values for unmasked oxygen saturation while still on supplemental oxygen therapy‡
3. Highest daily FiO_2‡
4. Duration of supplemental oxygen exposure‡
5. Documentation of post-discharge oxygen use

Follow Up data –

1. Anthropometric measurements at 18-22months corrected age
2. Neuro-developmental follow up at 18-22 months corrected age

Primary Outcome:

Growth in-hospital and at 18-22 months corrected age and in-hospital growth trajectories in high and low saturation arms.

Sample Size:

Given the importance of using an RCT to establish the impact of different levels of oxygen saturation from birth on short and long term growth, and recognizing the wealth of oxygen saturation data that will be available for analysis combined with the absence of comparable data in the literature, all infants in the SUPPORT Trial should be recruited into this secondary (n=1320). This sample size will be adequate to detect subtle differences in growth between the two groups with adequate ($\geq$80%) power. For example, this sample size will have at least 80% power to detect a difference in means between the two saturation groups of less than 40 g (assuming a mean weight of 1000 g in the control group and a standard deviation of 250 g) using a two group t-test with a 0.05 two-sided significance level.

Statistical Analysis:

Based upon intent-to-treat, differences between treatment arms with respect to continuous outcomes (such as weight, length, etc.) will be assessed by the Student t-test or the Mann-Whitney U-test, depending upon whether the empirical distribution of the data is approximately normal or heavily skewed. Adjusted analyses will be conducted using

linear regression to determine the relationship between measures of oxygen saturation and growth in the presence of covariates and confounders (such as site, gestational age, gender, etc.). Categorical outcomes (such as BPD, growth failure, etc.) will be compared across treatment groups using the chi-square test. Logistic regression models will be developed to determine whether oxygen saturation independently affects growth after correction for confounding variables that also alter growth.

In-hospital growth data will be available over multiple points in time. Outcomes available from this temporal distribution will enable us to perform a longitudinal analysis comparing the trajectories of growth between the two treatment groups. Longitudinal studies are powerful both in terms of explanatory power and statistical efficiency. They are useful in examining whether children in the two different oxygen saturation arms have different developmental trajectories over time. Further, longitudinal studies are statistically more efficient since they acknowledge and account for naturally occurring differences among children, including unmeasured characteristics such as genetic make-up, prenatal exposures, etc.

In order to analyze longitudinal growth data we propose to use hierarchical modeling, where the first stage models growth as a function of time/child's age, and the second stage models this association as a function of each child's treatment status. This flexible modeling formulation allows each child to have its own unique developmental trajectory, which could depend on its treatment status.

Discussion of Anticipated Results

We anticipate a better growth outcome in-hospital and at 18-22 months corrected age in the infants randomized to the lower target saturation range who maintained their median oxygen saturations within study range. We further anticipate that longitudinal analyses will demonstrate that these infants will have a sustained higher trajectory of growth over time compared to infants in the higher target saturation range.

Budget:

Additional nursing time, needed to collect required anthropometric data and other data from chart review at discharge and at follow-up, is estimated to be 1 hour. The cost for the entire cohort (1320 subjects), at $32.00 per nursing hour, would be $42,220. Assuming a 35% mortality for this extremely preterm population (estimated from GDB), 858 subjects could be expected to survive to discharge and estimating time for survivors alone will reduce the budget to $27,456.00.

References:

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Askie LM, Henderon-Smart DJ. Cochrane Review "Restricted versus liberal exposure for preventing morbidity and mortality in preterm or low birth weight infants", last updated October 2003.

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Cooke RJ, Ainsworth SB, Fenton AC. Postnatal growth retardation: a universal problem in preterm infants. Arch Dis Child Fetal Neonatal Ed 2004; 89: F428-F430

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Hudak BB, Allen MC, Hudak ML, Loughlin GM. Home oxygen therapy for CLD in ELBW infants. AJDC 1989; 143: 357-360

Lemons JA, Bauer CR, et al for NICHD Neonatal Research Network. Very low birth weight outcomes of the National Institute of Child Health and Development Neonatal Research Network, January 1995 through December 1996. Pediatrics 2001; 107(1)

Markestad T, Fitzhardinge PM: Growth and development in children recovering from BPD. J Pediatr 1981;98:597-602

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Tin W, Milligan DWA, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001; 84: F106-110

From: Michael O`Shea
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT GROWTH SECONDARY
Date: Tuesday, September 20, 2005 4:31:54 PM

2) Yes - go forward; use 2006 funds
Mike

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 20, 2005 4:25 PM
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O`Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
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From: Neil Finer
To: "Angelita Hensman"; "Das, Abhik"; "Schaefer, Scott E."
Cc: "Abbot Laptook"; Higgins, Rosemary (NIH/NICHD) [E]; "Hastings, Betty J."; "Zaterka-Baxter, Kristin"
Subject: RE: SUPPORT study baby too small for GDB
Date: Tuesday, September 20, 2005 1:22:51 PM

Hi Angelita
I hope this baby does well. Thanks for the effort to enroll this family in SUPPORT. You could set a record here!!!
Neil

From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Tuesday, September 20, 2005 8:11 AM
To: Das, Abhik; Schaefer, Scott E.
Cc: Abbot Laptook; higginsr@mail.nih.gov; Hastings, Betty J.; Zaterka-Baxter, Kristin; nfiner@ucsd.edu
Subject: SUPPORT study baby too small for GDB

Hi Abhik and Scott,
We enrolled a mom who delivered at 24 weeks 3 days into the SUPPORT study (sectioned for PIH) . The baby was IUGR and weighed 370 grams at birth and is not eligible for the Generic Data Base and therefore does not get a GDB Network Number. Don't we need to collect GDB data on this baby and how do we enter the Support Study forms into the data entry system without a Network Number? Please advise.
Thanks
Angelita

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; npeters@wfubmc.edu; nfiner@ucsd.edu
Cc: wrich@ucsd.edu; bkh@rti.org; kzaterka@rti.org; moshea@wfubmc.edu
Subject: Re: SUPPORT baby
Date: Monday, September 19, 2005 9:37:10 PM

Great news!
Wally
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
To: Nancy Peters <npeters@wfubmc.edu>; Neil Finer <nfiner@ucsd.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>
CC: wrich@ucsd.edu <wrich@ucsd.edu>; Hastings, Betty J. <bkh@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Michael O`Shea <moshea@wfubmc.edu>
Sent: Mon Sep 19 14:59:32 2005
Subject: RE: SUPPORT baby

TERRIFIC!!!
Thanks

Rose

From: Nancy Peters [mailto:npeters@wfubmc.edu]
Sent: Monday, September 19, 2005 3:58 PM
To: Neil Finer; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD)
Cc: wrich@ucsd.edu; Hastings, Betty J.; Zaterka-Baxter, Kristin; Michael O`Shea
Subject: SUPPORT baby

Just a note to let you know that we have officially enrolled our first child in the SUPPORT study (b) (6) (b) (6) -about 2pm. The infant was 24.2wks GA, 594 gms, randomized to the CPAP arm and all went well. We were lucky as the RTT on duty had been the staff person that attended the session in Cincinnati. She said she was pleasantly surprised at how it went, that it went smoother that she had expected, that the baby was down to the nursery within 8 minutes of delivery, and that the child has continued to do well on CPAP. There was a little (okay, more than a little) grumbling from the nursing staff that wanted to take the baby off of CPAP to weigh, etc but that is something we can work on. I will have to admit that we did not cover that as well in our orientation of the staff and that perhaps it would be helpful to them if we weigh all of the various hats, prongs, tubes and provide them with that information on a little card so they can then just subtract those weights to obtain the corrected weight of the infant.

Please let me know if you have any questions.

Nancy P.

From: Duara, Shahnaz
To: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]
Subject: growthprot revised Aug 9 2005.doc
Date: Monday, September 12, 2005 4:14:28 PM
Attachments: growthprot revised Aug 9 2005.doc

Hi Neil and Rose,

Will the protocol for the SUPPORT Growth secondary be circulated to the PIs before the meeting? The presentation time is brief so allowing them to read it ahead of the meting would make it easier for me.

Thanks
Shahnaz
<<growthprot revised Aug 9 2005.doc>>

Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study: A Proposed Secondary Study

Cristina Navarrete MD, and Shahnaz Duara MD
University of Miami Miller School of Medicine, Miami, FL.

Abstract:

Post-natal growth restriction is a major problem in preterm infants. Perturbations in oxygenation are recognized to influence post-natal growth; hypoxic conditions can directly impair growth and hyperoxic conditions predispose infants to BPD, which in turn has been linked to poor growth. The NICHD Neonatal Network is conducting a prospective trial of preterm infants randomized to two levels of baseline oxygen saturations. The effect of baseline saturations on pulmonary morbidity and ROP are the primary outcome measures. With respect to post-natal growth, there is a paucity of data relating alterations in baseline oxygen saturation and/or frequent deviations above or below the baseline to growth outcomes. We propose a secondary study to quantify short-term growth velocity in-hospital and long-term growth at 18-22 months of corrected age for infants enrolled in the SUPPORT Trial in relationship to oxygen saturation.

A. Hypothesis to be tested

Primary:

1. Infants in the low oxygen saturation group (85-89%) will have better in-hospital and long-term (18-22 months corrected age) growth.

2. Trajectories of growth in hospital will be better for infants in the low oxygen saturation group.

Secondary:

1. Growth will be greater in infants who spend > 50% of the time with daily median oxygen saturation between 85% -95% while on supplemental oxygen, independent of randomization to low or high oxygen saturation.

2. Infants with BPD will have poorer in-hospital and long-term growth than infants without BPD, independent of the saturation randomization arm.

3. Better long-term growth will be positively related to neuro-developmental outcome, independent of the saturation randomization arm.

B. Specific Aims:

1. To determine anthropometric measurements (wt, HC, length) in infants randomized to low and high oxygen saturation arms, from birth to hospital discharge and again at 18-22 months corrected age.
2. To determine nutritional intake (parenteral and enteral) during hospital stay.
3. To determine the percentage of infants with growth <10 percentile at 36 weeks PMA or discharge, whichever comes first.
4. To determine the percentage of infants with growth <10 percentile at 18-22 months corrected age.
5. To determine growth in relation to the proportion of time spent with oxygen saturation
    a. <85% and >95%
    b. 85%-95%
6. To determine growth in relation to infants' median oxygen saturation while in supplemental oxygen
    a. median oxygen saturation > 95%
    b. median oxygen saturation 85% - 95%
    c. median oxygen saturation < 85%
7. To relate incidence of BPD in low and high saturation arms to growth.
8. To determine in-hospital growth velocity/trajectory in low and high saturation arms.
9. To determine long-term growth velocity/trajectory, from hospital discharge to follow up at 18-22 months corrected age in low and high saturation arms.
10. To relate neuro-developmental outcome at 18-22 months corrected age to long-term growth in low and high saturation arms.

Rationale:

The SUPPORT Trial will randomize infants to two ranges of SpO2 in order to test the hypothesis that use of a lower SpO2 range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity and/or the need for surgical intervention. Retrospective cohort data from several units in the U.K., with different oxygen supplementation policies, revealed poorer growth patterns in the preterm infants exposed to higher oxygen saturations for the duration of oxygen exposure (Tin 2001). Conversely, observational data of infants with established BPD show better growth with home oxygen support (Groothius 1987), and two recent RCT of different target saturations in older oxygen-dependent premature infants showed no difference in short or long-term growth outcomes (STOP-ROP 2000, BOOST Trial 2003). There are no RCT data evaluating the short or long-term growth impact of different SpO2 strategies with supplemental oxygen use in a birth cohort of extremely preterm infants. Therefore, this study provides an opportunity for us to

obtain critically needed growth information on premature infants who are exposed from birth to different target oxygen saturation strategies.

Background

Improvements in antenatal care, respiratory support and nutrition have contributed to increased survival of ELBW infants. As the number of survivors increase, the long term outcome of these infants becomes more important. Lemons et al described growth failure or weight <10th percentile at 36 weeks postmenstrual age in 97% of ELBW infants surviving to discharge. Some morbidities in adulthood are linked to growth during the early post-natal period (Singhal 2004) and make adequacy of growth in this population of heightened interest.

Instead of following intra-uterine growth curves of age matched fetuses, VLBW infants exhibit wide-spread post-natal growth retardation (Cooke 2004), losing ground during the first weeks of life (Berry 1997). To resume growth post-natally, nutrition is of paramount importance; however, other factors such as severity of illness and perhaps oxygenation also play a role. Observational studies of infants with BPD showed poor post-natal growth when infants were sent home without oxygen supplementation (Markestad 1981).

Although preterm infants without lung disease attain oxygen saturations >95%, artificial attempts to keep arterial oxygenation at a "physiological" level may not be beneficial to growth, the lung or retina (Tin 2001). Animal studies have shown that newborn mammals (mice, rats, guinea pigs) develop poor growth with chronic hypoxia and that blunted body growth is directly proportional to the profundity of the exposure to chronic hypoxia (Mortola 1990). Chronic hypoxemia has also been suggested as the cause of poor growth in patients with cyanotic congenital heart disease (Dundar 2000). When home oxygen supplementation was discontinued inappropriately by parents in a cohort of VLBW infants with BPD, there was a deceleration in the rate of weight gain, which improved when oxygen supplementation was resumed (Groothius 1987). Hudak et al in 1989 observed that ELBW infants with CLD who went home on oxygen supplementation had good catch-up growth at 19 months. Taken collectively, these data suggest that hypoxic conditions affect growth negatively and supplementing oxygen may improve growth.

The optimal level of oxygen saturation to promote post-natal growth is unknown. Most of the available human data is limited to oxygen supplementation of infants who are oxygen dependent or have BPD. Baraldi et al demonstrated that discharged infants with BPD, who were kept on supplemental oxygen to keep saturations above 94%, had progressive but poor weight gain (stayed below 3rd percentile) at 9 months corrected age follow-up. In infants with BPD whose oxygen supplementation was intentionally discontinued, the subset who exhibited episodes of desaturations below 88-91% had a significant decline in the rate of weight gain as compared to those who maintained saturations above 92% (Moyer-Mileur 1996). Conversely, when two different oxygen saturation control policies (high: 88-98% and low: 70-90%) were retrospectively reviewed in <28

week gestation infants, the infants being cared for in the high oxygen saturation policy units were more likely to weigh less than the 3rd percentile at discharge (45% vs. 17%, Tin 2001). The infants assigned to the high oxygen saturation limits were also more likely to have BPD and ROP.

Recently, the BOOST Trial demonstrated that randomizing infants born <30 weeks gestation who were still on oxygen at 32 weeks postmenstrual age either to standard saturations (91-94%) or to high saturations (95-98%) produced no significant difference in growth at 12 months corrected age. This study, while randomizing infants to two different levels of saturations (conventional and high), only enrolled infants if they were still on oxygen supplementation at 32 weeks PMA and used higher limits than planned by SUPPORT. Our proposal is novel in that randomization to the two oxygen strategies begins at birth and continues for as long as the infants are in supplemental oxygen - by implementing this secondary we will be able to determine the impact of these strategies on short and long-term growth.

Methods:

Anthropometric Measures – at birth, postnatal days 7, 14, 21, and 28 days, 32 w PMA and 36 w PMA or discharge (wt, length, HC)

1. Weight - using standard digital electronic scales (c/o infant's nurse)
2. Length - using the Premie Length Board (average of two values, c/o research staff)
3. Head circumference - using paper measurement tape (average of c/o research staff)

Clinical Data-

1. Date when infant regains birth weight
2. Date of first enteral feed
3. Date of full enteral feeds (enteral > 120ml/kg/d)
4. Total number of days on parenteral nutrition
5. 24 h intake 'snapshots' (Parenteral, Enteral) – postnatal days 7, 14, 21, and 28, 32w PMA, 36w PMA or discharge (whichever comes first)
6. Presence of BPD

Intervention Data –

1. Duration of time spent in target saturation ranges of interest (Already part of SUPPORT‡)
2. Median values for unmasked oxygen saturation while still on supplemental oxygen therapy‡
3. Highest daily FiO_2‡
4. Duration of supplemental oxygen exposure‡
5. Documentation of post-discharge oxygen use

Follow Up data –

1. Anthropometric measurements at 18-22months corrected age
2. Neuro-developmental follow up at 18-22 months corrected age

Primary Outcome:

Growth in-hospital and at 18-22 months corrected age and in-hospital growth trajectories in high and low saturation arms.

Sample Size:

Given the importance of using an RCT to establish the impact of different levels of oxygen saturation from birth on short and long term growth, and recognizing the wealth of oxygen saturation data that will be available for analysis combined with the absence of comparable data in the literature, all infants in the SUPPORT Trial should be recruited into this secondary (n=1320). This sample size will be adequate to detect subtle differences in growth between the two groups with adequate ($\geq$80%) power. For example, this sample size will have at least 80% power to detect a difference in means between the two saturation groups of less than 40 g (assuming a mean weight of 1000 g in the control group and a standard deviation of 250 g) using a two group t-test with a 0.05 two-sided significance level.

Statistical Analysis:

Based upon intent-to-treat, differences between treatment arms with respect to continuous outcomes (such as weight, length, etc.) will be assessed by the Student t-test or the Mann-Whitney U-test, depending upon whether the empirical distribution of the data is approximately normal or heavily skewed. Adjusted analyses will be conducted using linear regression to determine the relationship between measures of oxygen saturation and growth in the presence of covariates and confounders (such as site, gestational age, gender, etc.). Categorical outcomes (such as BPD, growth failure, etc.) will be compared across treatment groups using the chi-square test. Logistic regression models will be developed to determine whether oxygen saturation independently affects growth after correction for confounding variables that also alter growth.

In-hospital growth data will be available over multiple points in time. Outcomes available from this temporal distribution will enable us to perform a longitudinal analysis comparing the trajectories of growth between the two treatment groups. Longitudinal studies are powerful both in terms of explanatory power and statistical efficiency. They are useful in examining whether children in the two different oxygen saturation arms have different developmental trajectories over time. Further, longitudinal studies are statistically more efficient since they acknowledge and account for naturally occurring differences among children, including unmeasured characteristics such as genetic make-up, prenatal exposures, etc.

In order to analyze longitudinal growth data we propose to use hierarchical modeling, where the first stage models growth as a function of time/child's age, and the second stage models this association as a function of each child's

treatment status. This flexible modeling formulation allows each child to have its own unique developmental trajectory, which could depend on its treatment status.

Discussion of Anticipated Results

We anticipate a better growth outcome in-hospital and at 18-22 months corrected age in the infants randomized to the lower target saturation range who maintained their median oxygen saturations within study range. We further anticipate that longitudinal analyses will demonstrate that these infants will have a sustained higher trajectory of growth over time compared to infants in the higher target saturation range.

Budget:

Additional nursing time, needed to collect required anthropometric data and other data from chart review at discharge and at follow-up, is estimated to be 1 hour. The cost for the entire cohort (1320 subjects), at $32.00 per nursing hour, would be $42,220. Assuming a 35% mortality for this extremely preterm population (estimated from GDB), 858 subjects could be expected to survive to discharge and estimating time for survivors alone will reduce the budget to $27,456.00.

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From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT time in target range
Date: Monday, September 12, 2005 3:52:10 PM

Hi Rose
I think that this is very helpful. I am trying to get the DR room air vs oxygen protocol ready to give to Richard, but that won't be an issue for any agenda.
See you Wednesday
Be well
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 12, 2005 12:26 PM
To: 'nfiner@ucsd.edu'
Subject: Fw: SUPPORT time in target range

Neil, did you need anything else from RTI for the meeting or is this it?
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Gantz, Marie <mgantz@rti.org>
To: nfiner@ucsd.edu <nfiner@ucsd.edu>
CC: Poole, W. Kenneth <poo@rti.org>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; wrich@ucsd.edu <wrich@ucsd.edu>
Sent: Mon Sep 12 14:19:20 2005
Subject: RE: SUPPORT time in target range

<<Pct in display range (supp O2) 9-12-05.rtf>>
Attached are the latest numbers for the percent of time babies are kept in their target O2 ranges. The numbers are for the High and Low O2 groups combined, and include only days on which the babies were known to be on supplemental O2. All study days 1+ are included.

Marie

Marie Gantz, Ph.D.

Research Statistician

RTI International

P.O. Box 12194

Research Triangle Park, NC 27709-2194

Telephone (919) 485-7780

Fax (919) 485-7762

mgantz@rti.org

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, September 12, 2005 12:43 PM
To: Gantz, Marie
Cc: Poole, W. Kenneth; 'Higgins, Rosemary (NIH/NICHD)'; wrich@ucsd.edu
Subject: RE: SUPPORT time in target range

Hi Marie

Do you have any more recent data regarding the downloads and SUPPORT? If so I would like to present to the Steering Committee

Thanks

Neil Finer

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, July 18, 2005 10:15 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu
Cc: Poole, W. Kenneth; Das, Abhik
Subject: SUPPORT time in target range

Attached are updated tables for the SUPPORT pulse oximeter data time in target range.

Marie

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-----Original Message-----
From: Gantz, Marie
Sent: Friday, June 24, 2005 12:09 PM
To: 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'
Cc: Poole, W. Kenneth; Das, Abhik
Subject: RE: SUPPORT time in target range

Attached are updated tables for the pulse oximeter data time in target range. If you would like an update of the gap analysis as well, I can get that to you next week (just let me know). Please let me know how often you would like to receive these updates. Every two weeks?

Thanks,

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-----Original Message-----
From: Gantz, Marie
Sent: Thursday, June 02, 2005 4:47 PM
To: 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'
Cc: Poole, W. Kenneth
Subject: RE: SUPPORT time in target range

Hi Neil and Wade,

Attached are two documents showing the proportion of time patients are kept

in the target pulse ox ranges at each center. The low and high cases are grouped together. In one document, the numbers are based on all the available pulse ox data. In the other, the numbers are only for days on which we know the babies spent time on supplemental O2. This determination is made using information from form SUPP05. If the baby was intubated/CPAP for >8 hours on a given day and the FiO2 value at 8:00, 16:00 or 23:59 was >.21 or if the baby was on cannula/hood for >8 on that day and FiO2 recorded closest to noon was >.21, then the baby was determined to be on supplemental O2 for that day.

As you will see, we could not identify many records corresponding to days spent on supplemental O2. There are a couple of reasons for this: (1) we have not received forms SUPP05 from some of the centers, (2) we only have information about supplemental O2 for the first 14 days of life, so pulse ox data for days 15 and higher are not included.

Please let me know if you have any questions.

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-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, May 24, 2005 5:38 PM
To: Gantz, Marie
Subject: RE: SUPPORT time in target range

Hello Marie

Many thanks for this data. I will circulate to the Subcommittee first and then decide how to best share with the sites.

Regards

Neil Finer

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, May 24, 2005 2:03 PM
To: wrich@ucsd.edu; nfiner@ucsd.edu
Cc: Poole, W. Kenneth
Subject: SUPPORT time in target range

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Date: Monday, September 12, 2005 2:19:28 PM
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PERCENT OF TIME SPENT IN EACH RANGE (OXIMETER DISPLAY)
DAYS ON SUPPLEMENTAL 02

Center Number	Total number of hours	<=85	>=85 and <88	TARGET >=88 and <=92	>92 and <=95	>95
3	6642.3	22.5	5.1	24.1	13.8	34.5
4	280.0	5.5	2.4	32.5	23.6	36.0
8	356.9	9.5	8.3	34.1	15.3	32.8
9	4984.6	18.3	6.9	35.0	11.6	28.3
11	3793.1	12.4	4.1	23.4	13.4	46.7
12	4729.9	14.0	7.1	32.8	17.2	28.9
13	641.5	5.9	5.4	32.7	10.1	46.0
14	12368.5	16.0	6.0	30.3	14.3	33.3
15	1.8	11.6	0.9	5.4	13.0	69.1
16	8806.5	18.9	8.1	41.4	11.1	20.4
18	779.6	16.1	2.2	14.2	17.6	50.0
19	9.1	2.4	0.5	4.9	6.2	86.0
22	8579.3	14.6	6.9	34.7	12.0	31.9
Total	**51973.1**	**16.6**	**6.4**	**32.1**	**13.3**	**31.6**

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Manual & Protocol
Date: Friday, September 09, 2005 3:14:42 PM

Hi Rose
I essentially said the same thing to Edmund, but will forward your wording to him.

Be well
Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 09, 2005 7:03 AM
To: Hastings, Betty J.; nfiner@ucsd.edu
Subject: RE: SUPPORT Manual & Protocol

How about
"As you know, this is an ongoing trial and we recommend appropriate discretion in discussions with scientific colleagues. We agree that common endpoints are important, but request that the information be used judiciously."

Neil – your thoughts??
Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Friday, September 09, 2005 8:02 AM
To: Higgins, Rosemary (NIH/NICHD); nfiner@ucsd.edu
Subject: FW: SUPPORT Manual & Protocol

Rose and Neil,
How do you think we should respond to his statement: You must let me know how much discretion your group want me to use in sharing the details of this with colleagues working on the strategy for the planned UK trial.
-----Original Message-----
From: Edmund Hey [mailto:(b) (6)
Sent: Friday, September 09, 2005 4:09 AM
To: Hastings, Betty J.
Cc: Finer, Neil
Subject: Re: SUPPORT Manual & Protocol

Thand you very much. Access to your full profocol will make it very much easier for us to ensure that the planned UK trial uses endpoints that can later be merged with those coming out of SUPPORT. You must let me know how much discretion your group want me to use in sharing the details of this with colleagues working on the strategy for the planned UK trial.

My address for any FedEx shipment should be
E Hey
(b) (6)
[redacted]
UK

> ----- Original Message -----
> **From:** Hastings, Betty J.

To: (b) (6)
Sent: Wednesday, September 07, 2005 9:39 PM
Subject: SUPPORT Manual & Protocol

Dr. Hey,
I will be glad to mail you a copy of the SUPPORT Manual and Protocol. Could you please send me your Fed-Ex address.
Thanks very much.
Betty

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

From: Miller, Lucy C.
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Hastings, Betty J.; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Med Watch
Date: Wednesday, September 07, 2005 4:06:53 PM

Great. Thanks,
Lucy

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 07, 2005 2:50 PM
To: Miller, Lucy C.
Cc: 'Hastings, Betty J.'; 'Zaterka-Baxter, Kristin'
Subject: RE: SUPPORT Med Watch

Thanks for getting back to me – it sounded like pulmonary hypoplasia. I will note it on the form.

Rose

From: Miller, Lucy C. [mailto:lucmille@iupui.edu]
Sent: Wednesday, September 07, 2005 3:25 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT Med Watch

Just wanted to let you know for the Med Watch for subject (b) (6) in the SUPPORT study, the clinicians did note pulmonary hypoplasia in the death note; although the death certificate is not in the medical record (I was waiting for that since I wasn't here when he was admitted and died) so I'm not sure what they've listed on that but it was in the note. Thanks,
Lucy

Blansfield, Earl (NIH/NICHD) [E]

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Wednesday, September 07, 2005 11:51 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Monica Collins
Cc: wrich@ucsd.edu
Subject: RE: Oxims

Ok. wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 07, 2005 10:10 AM
To: Wally Carlo, M.D.; Monica Collins
Cc: wrich@ucsd.edu
Subject: FW: Oxims

Monica or Wally -
Could you provide 2 blue oximeters to San Diego today??
Thanks
Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, September 07, 2005 11:02 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Oxims

Rose,
I have used all of my blue oximeters, including my extra stash.
I have a baby delivering today, at which time I will take Sharp's last blue. We could sure use a couple of blue oximeters if someone has them to spare. This delivery
will put us at 35 babies.
Thanks
Wade

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT-RA challenge
Date: Monday, August 29, 2005 12:22:49 PM

I finally got Michele's availability about an hour ago.

Should we schedule a 2 hour call with benchmarking...1hr for spr and the second for the smaller group to discuss?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 29, 2005 12:17 PM
To: Petrie, Carolyn
Subject: FW: SUPPORT-RA challenge

I think we were waiting for this for the call.
Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Monday, August 29, 2005 12:09 PM
To: Angelita Hensman; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD); wrich@ucsd.edu
Cc: Zaterka-Baxter, Kristin; Abbot Laptook
Subject: RE: SUPPORT-RA challenge

It is my understanding that Michele and Nancy will be working on the revisions to the forms and manual. I will check on the status of these.

-----Original Message-----
From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Monday, August 29, 2005 12:04 PM
To: nfiner@ucsd.edu; Das, Abhik; higginsr@mail.nih.gov; wrich@ucsd.edu
Cc: Zaterka-Baxter, Kristin; Hastings, Betty J.; Abbot Laptook
Subject: SUPPORT-RA challenge

Hi Folks,
We cannot start using the new RA challenge procedure for the SUPPORT study till we have it approved by our IRB and we need the updated manual (appendix) to do that. My understanding is that there were further revisions to be made to it after the last GDB conference call.

For now we have no choice but to code the infants who have reached 36 weeks and who are on vapotherm by the existing criteria. There have been 4 infants to date.

Thanks
Angelita

From: Nancy Peters
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: FYI
Date: Tuesday, August 23, 2005 5:09:46 PM

Rose,

I agree with Mike that this has been embarassing. We did discuss this somewhat on the last conference call--the delay in SUPPORT. It has been an unusual last few months with my staff out with illnesses (themselves and family) and vacation--and many days I found that I had to cover for three staff members. I had not planned to (b) (6) and delayed the start of Candida and SUPPORT. We are in the midst of interviewing for additional research staff and plan to add another full-time person dedicated to NICHD projects. We are committed to our NRN projects and have been pleased to find that our sites have showed a pride in having a connection to the NICHD, and an increased enthusiasm in participating in neonatal studies (teaching old dogs new tricks sometimes takes a bit of time).

Thank you for always making yourself available to answer our questions and give us your support. I can only hope for "five more years", but realize that our delay in getting started in these trials goes on the negative side of the score board for us. Perhaps we will rebound and be as successful with enrollment with SUPPORT as we have with PCV7.

Nancy

From: Michael O`Shea
Sent: Tuesday, August 23, 2005 3:39 PM
To: Nancy Peters
Subject: FYI

From: Michael O`Shea
Sent: Tuesday, August 23, 2005 3:39 PM
To: 'Higgins, Rosemary (NIH/NICHD)'
Subject: RE: enrollment

Rose,

This is embarrassing, but we have been IRB approved for both studies for at least a couple of months. I met with Nancy this morning she assures me that we will begin recruiting for Candida this week and SUPPORT on Monday August 29. I am sorry that we have been slow initiating these studies.

Mike

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 23, 2005 2:42 PM
To: Michael O`Shea
Subject: enrollment

Hi Mike,
On the latest monthly reports, there are no infants enrolled or screened either in the Candida Trial or the

SUPPORT Trial from the Wake Forest site. I confirmed this with the data center. I had thought you had IRB approval and were all set with these two studies. Can you let me know if this is not correct? If you do have IRB approval, let me know why there are infants screened.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Protocol
Date: Tuesday, August 23, 2005 12:32:37 PM

Rose
Great---we should share!
Seetha

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 22, 2005 2:52 PM
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: Petrie, Carolyn; Hastings, Betty J.; Zaterka-Baxter, Kristin
Subject: SUPPORT Protocol

Hi,
Dr. Finer has asked that Dr. Edmund Hey receive a copy of the SUPPORT protocol. Dr. Hey is leading the oximetry study in the UK. Since we recently voted to allow Dr. Tarnow-Mordi access, we will also allow Dr. Hey the same access.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: nfiner@UCSD.Edu
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT Protocol
Date: Tuesday, August 23, 2005 9:34:11 AM

> Hi Rose
Thanks
I vote that we share this will Edmund
Neil
>
> Dr. Finer has asked that Dr. Edmund Hey receive a copy of the SUPPORT
> protocol. Dr. Hey is leading the oximetry study in the UK. Since we
> recently voted to allow Dr. Tarnow-Mordi access, we will also allow Dr. Hey
> the same access.
>
> Thanks
>
> Rose
>
>
>
>
>
> Rosemary D. Higgins, M.D.
>
> Program Scientist for the Neonatal Research Network
>
> Pregnancy and Perinatology Branch
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> Center for Developmental Biology and Perinatal Medicine
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> 301-496-3790 (FAX)
>
> higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>
>
>
>
>

From:	Richard Ehrenkranz
To:	Higgins, Rosemary (NIH/NICHD) [E]; Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O"Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc:	Petrie, Carolyn; Hastings, Betty J.; Zaterka-Baxter, Kristin
Subject:	Re: SUPPORT Protocol
Date:	Monday, August 22, 2005 4:22:16 PM

That's fine with me.
Richard

At 02:51 PM 8/22/2005, Higgins, Rosemary (NIH/NICHD) wrote:

> Hi,
> Dr. Finer has asked that Dr. Edmund Hey receive a copy of the SUPPORT protocol. Dr. Hey is leading the oximetry study in the UK. Since we recently voted to allow Dr. Tarnow-Mordi access, we will also allow Dr. Hey the same access.
> Thanks
> Rose
>
> Rosemary D. Higgins, M.D.
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
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> 301-496-3790 (FAX)
> higginsr@mail.nih.gov

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT Protocol
Date: Monday, August 22, 2005 4:00:39 PM

---

aok with me
BJS

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
Medical Director, Children's Healthcare of Atlanta at Egleston
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

From:	Neil Finer
To:	ccole@bidmc.harvard.edu; Sue Hey; Peter Brocklehurst; Brian Darlow; Professor Colin Morley; william tarnow-mordi; Barbara Schmidt
Cc:	Ken Poole; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Donovan, Edward (DONOVAEF); Avroy A. Fanaroff, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich; Michele Walsh; Betty Hastings; Robin Roberts; Maribeth Sayre
Subject:	Re: No.of oximeters: simulation study for COT
Date:	Thursday, August 18, 2005 12:20:14 AM

Hi Barbara
Thanks for sharing this with us. At the present time the Network has access to about 250 oximeters and we are shipping from center to center using some depot centers as the need arises. I used your calculation and came up with 225 oximeters, about 25 less than we have at present. I hope these numbers work but I would caution you that the problem we have seen is multiple deliveries where we randomize all to one arm. Thus last night we needed [redacted] oximeters of the same skew for (b) (6) As you are allowing up to 18 hours from birth, this may be a buffer allowing for sharing but I doubt that this will work. In addition you have large distances to cover. We did our own calculations and initially thought that 225 would work and that was our initial supply, but we are not yet certain that when all centers enroll at peak efficiency that we will have enough. I think a 10% loss is acceptable, as we also have to obtain prenatal consent which probably has a greater failure than postnatal consent. We start the oximeter by 1 hour of age.
Lets keep in touch and see how the numbers work. I would guess that we will need up to 300 oximeters by the time we are at full capacity with 16 centers enrolling 1300 infants over 2 years. However, we discontinue the oximeter once the infant is in room air for 3 days and not on any respiratory support which may increase your needs relative to ours. We restart if the infant requires any support or oxygen.
Good luck.
Neil
----- Original Message -----
From: "Barbara Schmidt" <schmidt@mcmaster.ca>
To: "william tarnow-mordi" <williamt@westgate.wh.usyd.edu.au>; "Professor Colin Morley" <colin.morley@wch.org.au>; "Brian Darlow" <brian.darlow@chmeds.ac.nz>; "Peter Brocklehurst" <peter.brocklehurst@perinatal-epidemiology.oxford.ac.uk>; "Sue Hey" (b) (6) [redacted] >; <ccole@bidmc.harvard.edu>; "'Neil Finer'" <nfiner@ucsd.edu>
Cc: "Maribeth Sayre" <MSayre@masimo.com>; "Robin Roberts" <robertsr@mcmaster.ca>
Sent: Wednesday, August 17, 2005 1:16 PM
Subject: No.of oximeters: simulation study for COT

> Dear All:
> Prof. Robin Roberts did a fine simulation study to estimate the number
> of required study oximeters for our Canadian Oxygen Trial (COT) grant
> submission. We decided to share it with you, because some of you may
> still find it useful for your own planning.
> With best wishes and regards
> Barbara
>
>

From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT AND OXIMETERS
Date: Thursday, August 11, 2005 4:38:00 PM

(b) (6) .
Very jealous.....

Signed
Hard working in Atlanta

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
Medical Director, Children's Healthcare of Atlanta at Egleston
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

From: Richard Ehrenkranz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT FORMS AND MANUAL
Date: Thursday, August 11, 2005 4:16:18 PM

Yes.
Richard

At 09:22 AM 8/10/2005, you wrote:
>HI,
>We have had a request to share the SUPPORT data collection forms and
>manual with Dr. William Tarnow-Mordi and the BOOST 2 trial
>investigators. The reason for this request is to insure that, if meta
>analyses are done, data are collected from the trials in a similar, if not
>identical manner. The BOOST 2 trial has obtained funding. Please send
>me your YES/NO vote by August 22.
>
>Thanks
>Rose
>Rosemary D. Higgins, M.D.
>Program Scientist for the Neonatal Research Network
>Pregnancy and Perinatology Branch
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>

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Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support Oxims
Date: Thursday, August 11, 2005 1:20:41 PM

Rose,

Nancy Newman seemed a bit distraught at the idea of being a transfer center for oximeters, saying she did not have time. If you want to just have her purchase the oximeters and ship them one time to me, I will be the control site for that 10 oximeters as well . Since we all ship Next-Day anyway, it is probably immaterial where we are located.
wade

From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT FORMS AND MANUAL
Date: Thursday, August 11, 2005 12:12:28 PM

Rose
okay with me
Seetha

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, August 10, 2005 9:22 AM
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin; Betty
Subject: SUPPORT FORMS AND MANUAL

HI,
We have had a request to share the SUPPORT data collection forms and manual with Dr. William Tarnow-Mordi and the BOOST 2 trial investigators. The reason for this request is to insure that, if meta analyses are done, data are collected from the trials in a similar, if not identical manner. The BOOST 2 trial has obtained funding. Please send me your YES/NO vote by August 22.

Thanks
Rose
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From: Michael O`Shea
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT FORMS AND MANUAL
Date: Thursday, August 11, 2005 10:41:33 AM

yes
Mike

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wed 8/10/2005 9:22 AM
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O`Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin; Betty
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Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Abbot Laptook
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: William Oh
Subject: RE: SUPPORT FORMS AND MANUAL
Date: Thursday, August 11, 2005 6:21:21 AM

---

yes

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, August 10, 2005 9:22 AM
To: Abbot Laptook; Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
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Thanks
Rose
Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
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(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT Trial Contact List 1_20_05
Date: Thursday, August 11, 2005 4:27:04 PM
Attachments: SUPPORT Trial Contact List 1_20_05.doc

<<SUPPORT Trial Contact List 1_20_05.doc>>

SUPPORT Trial Contact List 1_20_05

SUPPORT Trial Contact List

Case Western
Center 3

Study PI Dr. Michele Walsh Email: mcw3@cwru.edu Phone: (216) 844-3387	**Respiratory Therapist** Mike Tracey RT Email: Michael.Tracy@uhhs.com Phone: (216) 844-1922
Study Coordinator Nancy Newman RN Email: nxs5@cwru.edu Phone:216-368-3084	**Research Nurses** Bonnie Siner RN Email: bss5@cwru.edu Phone: 216-368-3066

SUPPORT Trial Contact List

UT-Dallas
Center 4

Study PI Dr. Walid Salhab Email: Walid.Salhab@utsouthwestern.edu Phone: 214 648 3753	**Respiratory Therapist** James Allen Email: JRALLE@parknet.pmh.org Phone: 214 590 8193 and 972.396.1920
Study Coordinator Gaynelle Hensley Email:gaynelle.hensley@utsouthwestern.edu Phone:214-648-3780	**Research Nurses** Della Feeha Email: DFEEHA@parknet.pmh.org Phone:214 590 6500

SUPPORT Trial Contact List

Wayne State
Center 5

Study PI Dr. Seetha Shankaran Email: sshankar@med.wayne.edu Phone: 313-745-1436	**Respiratory Therapist** Rontriece Turner Email: rturner@dmc.org Phone: 313-745-1501 George Benvenuto Email: gbenvenuto@dmc.org Phone: 313-745-1510
Study Coordinator Rebecca Bara Email: ae5357@wayne.edu Phone:313-745-1436	**Research Nurses**

SUPPORT Trial Contact List

Miami
Center 8

Study PI Dr. Shahnaz Duara Email: sduara@miami.edu Phone: (305) 585-6408	**Respiratory Therapist** Lucille Fasone Email: lfasone@um-jmh.org Phone: 305-585-5147
Study Coordinator Ruth Everett Email: reverett@med.miami.edu Phone:305-585-8433	**NICU Nurse** Barbara Burke Email: bburke@um-jmh.org Phone: 305-585-5676

SUPPORT Trial Contact List

Emory
Center 9

Study PI Dr. Susie Buchter Email: susie.buchter@oz.ped.emory.edu Phone: (404) 778-1413	**Respiratory Therapist** Irma Seabrook, RRT Email: iseabrook@gmh.edu or (b) (6) [redacted] Phone: 404-616-2279
Study Coordinator Ellen Hale Email: ellen_hale@oz.ped.emory.edu Phone:404-616-4218	**Research Nurses** Email: Phone:

SUPPORT Trial Contact List

Cincinnati
Center 11

Study PI Dr. Vivek Narendran Email: Vivek.Narendran@cchmc.org Phone: (513) 558-0557 Kurt Schibler Email: kurt.schibler@cchmc.org Phone: (513) 636-3972	**Respiratory Therapist** Sandy McClanahan Email: Phone: Dave Mane Email: Phone: Eric Stephenson Email: Phone:
Study Coordinator Cathy Grisby Email: grisbyca@email.uc.edu Phone: (513) 558-4953	**Research Nurses** Pam Krieg Deb Riedinger Bonnie Eilerman Pasty Uebel

SUPPORT Trial Contact List

Indiana
Center 12

Study PI Dr. James Lemons Email: jlemons@iupui.edu Phone: (317) 274-4716	**Respiratory Therapist** Mitsy Halbert RRT Email: mhalbert@clarian.org Beth Summit RRT Email: esummitt@clarian.org Phone:
Study Coordinator Lucy Miller Email: lucmille@iupui.edu Phone:317-278-7809	**Research Nurses**

SUPPORT Trial Contact List

Yale
Center 13

Study PI Dr. Vineet Bhandari Email: vineet.bhandari@yale.edu Phone: 203-688-2320	**Respiratory Therapist** Tim Mack RT Email:tim mack@ynhh.org Ginny.defilippo@ynhh.org Chief RT Phone:203-688-2201
Study Coordinator Pat Gettner Email: pat.gettner@yale.edu Phone: 203-688-7987	**Research Nurses** Monica Konstantino Email:pat.gettner@yale.edu Phone:203-688-7987 or 688-2318

SUPPORT Trial Contact List

Brown
Center 14

Study PI Dr. Abbot Laptook Email: alaptook@wihri.org Phone: (401) 274-1122 ext 1221	**Respiratory Therapist** Daniel Gingras E-mail: dgingras@wihri.org Phone: (401) 274-1122 ext 1435
Study Coordinator Angelita Hensman E- mail: ahensman@wihri.org Phone: (401) 274-1122 ext 1730	**Nurse (NICU Asst: Nurse Manager)** Kim Francis E-mail: kfrancis@wihri.org Phone: (401) 274-1122 ext 1324

SUPPORT Trial Contact List

Stanford
Center 15

Study PI Dr. Krisa Van Meurs Email: vanmeurs@leland.stanford.edu Phone: 650 723-5711	**Respiratory Therapist** Dan Proud Email:wproud@stanfordmed.org Phone: 650 4978015
Study Coordinator Bethany Ball Email: mbball@leland.stanford.edu Phone: (650) 725-8342	**Research Nurses** Email: Phone:

SUPPORT Trial Contact List

Alabama
Center 16

Study PI Dr. Wally Carlo Email: wcarlo@peds.uab.edu Phone: (205) 934-4680	**Respiratory Therapist** Robert Johnson Email: Phone:
Study Coordinator Monica Collins Email: mcollins@peds.uab.edu Phone:205-934-5771	**Research Nurses**

SUPPORT Trial Contact List

UT-Houston
Center 18

Study PI Dr. Brenda Morris Email: Brenda.H.Morris@uth.tmc.edu Phone:	**Respiratory Therapist** Clint Kneuven Email: Clint_Kneuven@mhhs.org Phone: 713-704-2900
Study Coordinator Georgia McDavid Email: Georgia.E.McDavid@uth.tmc.edu Phone: 713-500-5734	**Research Nurses** Kim Cole Email: Kim Cole Phone: 713-704-2900 Sandee Eisenbiez Email: Sandee_Eisenbiez@mhhs.org Phone: 713-704-2900 Jennifer Simmons Email: Jennifer_ Simmons@mhhs.org Phone: 713-704-2900

Duke
Center 19

Study PI Dr. C. Michael Cotten, MD Email: cotte010@mc.duke.edu Phone: (919) 681-0630	**Respiratory Therapist** John Heinz, RRT Email: heinz001@mc.duke.edu Pager: (919) 970-(b) [redacted]
Study Coordinator Kathy Auten Email: kathy.auten@duke.edu Phone: 919-681-5859	**Research Nurses** Kathy Foy, RN Email: foy00004@mc.duke.edu Phone: (919) 668-3360 Josette Collen, RN

SUPPORT Trial Contact List

Rochester
Center 21

Study PI Dr. Nirupama Laroia Email:Nirupama_laroia@urmc.rochester.edu Phone: (585) 275-2972	**Respiratory Therapist** Vince L. Romano RRT Email: Vince_Romano@urmc.rochester.edu Phone:
Study Coordinator Linda Reubens Email: linda_reubens@urmc.rochester.edu Phone: (585) 275-0218	**Research Nurses** Email: Phone:

SUPPORT Trial Contact List

UC-San Diego
Center 22

Study PI Dr. Neil Finer Email: nfiner@ucsd.edu Phone: (619) 543-3759	**Respiratory Therapist** Jim Goodmar Email: jgoodmar@ucsd.edu Phone: 619-543-3801
Study Coordinator Wade Rich Email: wrich@ucsd.edu Phone: 619-543-5375	**Research Nurses** Renee Bridge Email: rbridge@ucsd.edu Phone: 619-543-6276

SUPPORT Trial Contact List

Wake Forest
Center 20

Study PI Dr. T. Michael O'Shea Email: moshea@wfubmc.edu Phone: (336) 716-2529	**Respiratory Therapist** Jennifer Griffin, RRT, RCP Email: jegriffi@wfubmc.edu Phone: (336) 713-6779 Joy Bowles, RRT, RCP Email: (b) (6) Phone: (336) 718-3160
Study Coordinator Nancy Peters Email: npeters@wfubmc.edu Phone: (336) 716-6911	**Research Nurses** Alice Scott, RN Email: ajscott@wfubmc.edu Phone: (336) 716-1240 Nancy Bivona, RN Email: nbivona@wfubmc.edu Phone: (336) 718-3091

SUPPORT Trial Contact List

RTI International
Data Coordinating Center

Study PI Dr. Ken Poole Email: poo@rti.org Phone: 919-485-7721	**Alternate Study PI** Dr. Abhik Das Email: adas@rti.org Phone: 301-770-8214
NICHD Liaison Coordinator Carolyn Petrie Email: petrie@rti.org Phone: 301-230-4648	**Protocol Coordinator** Betty Hastings Email:bkh@rti.org Phone: 919-485-7740

SUPPORT Trial Contact List

NICHD

Program Scientist
Dr. Rosemary Higgins
Email: higginsr@mail.nih.gov
Phone: 301-435-7909

From: Charles Rosenfeld
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT FORMS AND MANUAL
Date: Wednesday, August 10, 2005 2:54:43 PM

---

yes

Charles R. Rosenfeld, M.D.
George L. MacGregor Professor of Pediatrics
and Professor of Obstetrics and Gynecology
Director, Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd.
Dallas, TX 75390-9063
Telephone: (214) 648-3903
FAX: (214) 648-2481
Email: charles.rosenfeld@utsouthwestern.edu

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 08/10/05 8:22 AM >>>
HI,

We have had a request to share the SUPPORT data collection forms and manual with Dr. William Tarnow-Mordi and the BOOST 2 trial investigators. The reason for this request is to insure that, if meta analyses are done, data are collected from the trials in a similar, if not identical manner. The BOOST 2 trial has obtained funding. Please send me your YES/NO vote by August 22.

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

From:	Wally Carlo, M.D.
To:	Higgins, Rosemary (NIH/NICHD) [E]; alaptook@WIHRI.org; adas@rti.org; bpoindex@iupui.edu; crosen@mednet.swmed.edu; dale_phelps@urmc.rochester.edu; Edward.Donovan@cchmc.org; richard.ehrenkranz@yale.edu; jobea0@chmcc.org; jlemons@iupui.edu; moshea@wfubmc.edu; mcw3@po.CWRU.edu; nfiner@ucsd.edu; William_oh@brown.edu; poo@rti.org; goldb008@mc.duke.edu; sduara@miami.edu; s_shankaran@wayne.edu; dstevenson@stanford.edu; barbara_stoll@oz.ped.emory.edu; Jon.E.Tyson@uth.tmc.edu; Walid.Salhab@UTsouthwestern.edu
Cc:	petrie@rti.org; kzaterka@rti.org; BKH@rti.org
Subject:	Re: SUPPORT FORMS AND MANUAL
Date:	Wednesday, August 10, 2005 12:20:03 PM

I vote YES, I think we should collaborate to make the data collection consistent
Wally
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
To: Abbot Laptook (alaptook@WIHRI.org) <alaptook@WIHRI.org>; Abhik Das <adas@rti.org>; Brenda Poindexter <bpoindex@iupui.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Charles Rosenfeld <crosen@mednet.swmed.edu>; Dale Phelps <dale_phelps@urmc.rochester.edu>; Ed Donovan <edward.donovan@cchmc.org>; Ehrenkranz Richard (E-mail) <richard.ehrenkranz@yale.edu>; Jobe Alan (E-mail) <Jobea0@chmcc.org>; Lemons Jim (E-mail) <jlemons@iupui.edu>; Michael O'Shea <moshea@wfubmc.edu>; Michelle Walsh <mcw3@po.cwru.edu>; Neil Finer <nfiner@ucsd.edu>; Oh William (E-mail) <william_oh@brown.edu>; Poole Kenneth (E-mail) <poo@rti.org>; Ronald GOldberg <goldb008@mc.duke.edu>; Shahnaz Duara <sduara@miami.edu>; Shankaran Seetha (E-mail) <s_shankaran@wayne.edu>; Stevenson David (E-mail) <dstevenson@stanford.edu>; Stoll Barbara (E-mail) <barbara_stoll@oz.ped.emory.edu>; Tyson Jon (E-mail) <Jon.E.Tyson@uth.tmc.edu>; Walid Salhab (Walid Salhab) <Walid.Salhab@UTsouthwestern.edu>
CC: Petrie, Carolyn <petrie@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Betty <BKH@rti.org>
Sent: Wed Aug 10 08:22:29 2005
Subject: SUPPORT FORMS AND MANUAL

HI,

We have had a request to share the SUPPORT data collection forms and manual with Dr. William Tarnow-Mordi and the BOOST 2 trial investigators. The reason for this request is to insure that, if meta analyses are done, data are collected from the trials in a similar, if not identical manner. The BOOST 2 trial has obtained funding. Please send me your YES/NO vote by August 22.

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

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(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Brenda Poindexter
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT FORMS AND MANUAL
Date: Wednesday, August 10, 2005 12:06:20 PM

Indiana votes YES – both to this request – and to Michele's request to share the forms and MOP for the physiologic definition.
Brenda

HI,
We have had a request to share the SUPPORT data collection forms and manual with Dr. William Tarnow-Mordi and the BOOST 2 trial investigators. The reason for this request is to insure that, if meta analyses are done, data are collected from the trials in a similar, if not identical manner. The BOOST 2 trial has obtained funding. Please send me your YES/NO vote by August 22.

Thanks
Rose
Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT FORMS AND MANUAL
Date: Wednesday, August 10, 2005 12:06:00 PM

---

yes

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

08/10/2005 09:22 AM

To: "Abbot Laptook (alaptook@WIHRI.org)" <alaptook@WIHRI.org>, Abhik Das <adas@rti.org>, Brenda Poindexter <bpoindex@iupui.edu>, "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>, Charles Rosenfeld <crosen@mednet.swmed.edu>, Dale Phelps <dale_phelps@urmc.rochester.edu>, Ed Donovan <edward.donovan@cchmc.org>, "Ehrenkranz Richard (E-mail)" <richard.ehrenkranz@yale.edu>, "Jobe Alan (E-mail)" <Jobea0@chmcc.org>, "Lemons Jim (E-mail)" <jlemons@iupui.edu>, "Michael O'Shea" <moshea@wfubmc.edu>, Michelle Walsh <mcw3@po.cwru.edu>, Neil Finer <nfiner@ucsd.edu>, "Oh William (E-mail)" <william_oh@brown.edu>, "Poole Kenneth (E-mail)" <poo@rti.org>, Ronald GOldberg <goldb008@mc.duke.edu>, Shahnaz Duara <sduara@miami.edu>, "Shankaran Seetha (E-mail)" <s_shankaran@wayne.edu>, "Stevenson David (E-mail)" <dstevenson@stanford.edu>, "Stoll Barbara (E-mail)" <barbara_stoll@oz.ped.emory.edu>, "Tyson Jon (E-mail)" <Jon.E.Tyson@uth.tmc.edu>, "Walid Salhab (Walid Salhab)" <Walid.Salhab@UTsouthwestern.edu>
cc: "Petrie, Carolyn" <petrie@rti.org>, "Zaterka-Baxter, Kristin" <kzaterka@rti.org>, Betty <BKH@rti.org>
Subject: SUPPORT FORMS AND MANUAL

HI,
We have had a request to share the SUPPORT data collection forms and manual with Dr. William Tarnow-Mordi and the BOOST 2 trial investigators. The reason for this request is to insure that, if meta analyses are done, data are collected from the trials in a similar, if not identical manner. The BOOST 2 trial has obtained funding. Please send me your YES/NO vote by August 22.

Thanks
Rose
Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
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MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT FORMS AND MANUAL
Date: Wednesday, August 10, 2005 10:55:20 AM

OK with me

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
Medical Director, Children's Healthcare of Atlanta at Egleston
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

From: Michele Walsh
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT FORMS AND MANUAL
Date: Wednesday, August 10, 2005 10:37:09 AM

Yes. MWalsh

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Abbot Laptook (alaptook@WIHRI.org) ; Abhik Das ; Brenda Poindexter ; Carlo Waldemar (E-mail) ; Charles Rosenfeld ; Dale Phelps ; Ed Donovan ; Ehrenkranz Richard (E-mail) ; Jobe Alan (E-mail) ; Lemons Jim (E-mail) ; Michael O'Shea ; Michelle Walsh ; Neil Finer ; Oh William (E-mail) ; Poole Kenneth (E-mail) ; Ronald GOldberg ; Shahnaz Duara ; Shankaran Seetha (E-mail) ; Stevenson David (E-mail) ; Stoll Barbara (E-mail) ; Tyson Jon (E-mail) ; Walid Salhab (Walid Salhab)
Cc: Petrie, Carolyn ; Zaterka-Baxter, Kristin ; Betty
Sent: Wednesday, August 10, 2005 9:22 AM
Subject: SUPPORT FORMS AND MANUAL

HI,
We have had a request to share the SUPPORT data collection forms and manual with Dr. William Tarnow-Mordi and the BOOST 2 trial investigators. The reason for this request is to insure that, if meta analyses are done, data are collected from the trials in a similar, if not identical manner. The BOOST 2 trial has obtained funding. Please send me your YES/NO vote by August 22.

Thanks
Rose
Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: nfiner@UCSD.Edu
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT FORMS AND MANUAL
Date: Wednesday, August 10, 2005 10:32:30 AM

>
I am OK with this
Neil
HI,
>
> We have had a request to share the SUPPORT data collection forms and manual
> with Dr. William Tarnow-Mordi and the BOOST 2 trial investigators. The
> reason for this request is to insure that, if meta analyses are done, data
> are collected from the trials in a similar, if not identical manner. The
> BOOST 2 trial has obtained funding. Please send me your YES/NO vote by
> August 22.
>
>
>
> Thanks
>
> Rose
>
> Rosemary D. Higgins, M.D.
>
> Program Scientist for the Neonatal Research Network
>
> Pregnancy and Perinatology Branch
>
> Center for Developmental Biology and Perinatal Medicine
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> NICHD, NIH
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>
> 301-435-7909
>
> 301-496-3790 (FAX)
>
> higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>
>
>
>
>

From:	Tyson, Jon E
To:	Edward Donovan; Oh William (E-mail); ALAN JOBE; Brenda Poindexter; Lemons Jim (E-mail); Higgins, Rosemary (NIH/NICHD) [E]; Ronald GOldberg; Charles Rosenfeld; Shahnaz Duara; Stoll Barbara (E-mail); Carlo Waldemar (E-mail); Michelle Walsh; Abhik Das; Poole Kenneth (E-mail); Stevenson David (E-mail); Neil Finer; Dale Phelps; Walid Salhab (Walid Salhab); Shankaran Seetha (E-mail); Michael O"Shea; alaptook@WIHRI.org; Ehrenkranz Richard (E-mail)
Cc:	Betty; Kristin Zaterka-Baxter; Carolyn Petrie
Subject:	RE: SUPPORT FORMS AND MANUAL
Date:	Wednesday, August 10, 2005 10:14:25 AM

Yes

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

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Wednesday, August 10, 2005 8:53 AM
To: Oh William (E-mail); ALAN JOBE; Brenda Poindexter; Lemons Jim (E-mail); Rosemary Higgins; Ronald GOldberg; Charles Rosenfeld; Shahnaz Duara; Stoll Barbara (E-mail); Carlo Waldemar (E-mail); Michelle Walsh; Abhik Das; Poole Kenneth (E-mail); Stevenson David (E-mail); Neil Finer; Dale Phelps; Tyson, Jon E; Walid Salhab (Walid Salhab); Shankaran Seetha (E-mail); Michael O'Shea; Abbot Laptook (alaptook@WIHRI.org); Ehrenkranz Richard (E-mail)
Cc: Betty; Kristin Zaterka-Baxter; Carolyn Petrie
Subject: Re: SUPPORT FORMS AND MANUAL

yes

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

"Conviction is a greater foe of truth than a lie."

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 08/10/2005 9:22:29 AM >>>
HI,
We have had a request to share the SUPPORT data collection forms and manual with Dr. William Tarnow-Mordi and the BOOST 2 trial investigators. The reason for this request is to insure that, if meta analyses are done, data are collected from the trials in a similar, if not identical manner. The BOOST 2 trial has obtained funding. Please send me your YES/NO vote by August 22.

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

NICHD, NIH
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MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT FORMS AND MANUAL
Date: Wednesday, August 10, 2005 9:30:19 AM

Yes
Shahnaz

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
To: Abbot Laptook (alaptook@WIHRI.org) <alaptook@WIHRI.org>; Abhik Das <adas@rti.org>; Brenda Poindexter <bpoindex@iupui.edu>; Carlo Waldemar (E-mail) <wcarlo@peds.uab.edu>; Charles Rosenfeld <crosen@mednet.swmed.edu>; Dale Phelps <dale_phelps@urmc.rochester.edu>; Ed Donovan <edward.donovan@cchmc.org>; Ehrenkranz Richard (E-mail) <richard.ehrenkranz@yale.edu>; Jobe Alan (E-mail) <Jobea0@chmcc.org>; Lemons Jim (E-mail) <jlemons@iupui.edu>; Michael O'Shea <moshea@wfubmc.edu>; Michelle Walsh <mcw3@po.cwru.edu>; Neil Finer <nfiner@ucsd.edu>; Oh William (E-mail) <william_oh@brown.edu>; Poole Kenneth (E-mail) <poo@rti.org>; Ronald GOldberg <goldb008@mc.duke.edu>; Shahnaz Duara <sduara@miami.edu>; Shankaran Seetha (E-mail) <s_shankaran@wayne.edu>; Stevenson David (E-mail) <dstevenson@stanford.edu>; Stoll Barbara (E-mail) <barbara_stoll@oz.ped.emory.edu>; Tyson Jon (E-mail) <Jon.E.Tyson@uth.tmc.edu>; Walid Salhab (Walid Salhab) <Walid.Salhab@UTsouthwestern.edu>
CC: Petrie, Carolyn <petrie@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Betty <BKH@rti.org>
Sent: Wed Aug 10 09:22:29 2005
Subject: SUPPORT FORMS AND MANUAL

HI,

We have had a request to share the SUPPORT data collection forms and manual with Dr. William Tarnow-Mordi and the BOOST 2 trial investigators. The reason for this request is to insure that, if meta analyses are done, data are collected from the trials in a similar, if not identical manner. The BOOST 2 trial has obtained funding. Please send me your YES/NO vote by August 22.

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Hastings, Betty J."
Subject: FW: Pulmonary follow up secondary to SUPPORT
Date: Tuesday, August 09, 2005 11:34:22 AM

Betty,
I did not see that these were cc'd to you. Can you forward them to Dr. Stevens?
Thanks,
wade

From: Yvonne Vaucher [mailto:yvaucher@ucsd.edu]
Sent: Friday, August 05, 2005 1:13 PM
To: mgfuller@ucsd.edu; wrich@ucsd.edu; 'Neil Finer'
Subject: RE: Pulmonary follow up secondary to SUPPORT

Martha/Wade: I agree that the data will be more accurately collected in person for our population and that telephone interviews for our population are particularly problematic due to language, suspicion, difficulty connecting. There are differences in scripted telephone vs less formal in-person interviews that might be cause for some statistical concern but I assume that issue has already been addressed by RTI.

My concerns are not so much about the kids who come to clinic, but about those who don't. Attempts at telephone contact for children who don't come to clinic (~ 20%) will be costly in time/effort. We need to be paid substantial extra $ if we do this instead of Rochester. Alternatively we could refer families that are difficult to contact to Rochester for them to pursue. Also contacting the PMD and cajoling the office to provide documentation of respiratory problems will also very be time-consuming and I am betting quite frustrating. The $25 "carrot" will not be persuasive for most providers given the time and effort to do the review and the PMD has no investment in the outcome (unlike the original Tucson docs).This aspect in particular should be done by Rochester. We are already at our limit trying to get kids into clinic. I think I would favor a hybrid approach...we do the questionnaire in clinic. If child does not come to clinic, then Rochester does the calls/recalls. In addition Rochester should be directly responsible for obtaining the medical record review (We could mail the request and ask the PMD to send the results directly to Rochester; Rochester should do the follow-up/ browbeating of the individual PMD offices to get the data. In terms of the medical record review we are an unnecessary middleman....an additional step/place to get things lost or confused.

Yvonne

---

1) Re: questionnaires these are better (still too wordy in my opinion) but an improvement.
2) I would like for us (actually, I guess it will be me since I'm in clinic) to administer the questionnaires. The more I work with our population the more convinced I am that it will be better to do this as part of our routine visits. The draft consent even includes as a benefit the early identification of breathing problems brought to the attention of the doctor.
3) Consent: Wade, do we already have IRB approval for the pulmonary f/u? If not, are you able to take that on? There is a draft consent attached. It seems to be relatively simplistic so it may meet our IRB standards. I am certain that in addition to the consent we will need to use the medical center approved release of records form to get permission to contact the md's for the information. Can that be attached to the consent?

Martha

Martha G. Fuller, RN, MSN

Pediatric Nurse Practitioner
UCSD Infant Special Care Follow-up Program
(619) 543-3771

From: Yvonne Vaucher [mailto:yvaucher@ucsd.edu]
Sent: Monday, August 01, 2005 11:08 AM
To: mgfuller@ucsd.edu
Subject: FW: Pulmonary follow up secondary to SUPPORT

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 01, 2005 5:35 AM
To: (apappas@med.wayne.edu); Anna Dusick (adusick@iupui.edu); Barbara Stoll (barbara_stoll@oz.ped.emory.edu); Betty Vohr ('Betty_Vohr@brown.edu'); Charlie Bauer (cbauer@peds.med.miami.edu); Dee WIlson (b) (6) Gary Myers (Gary_myers@URMC.Rochester.edu); Ira Adams-Chapman; Jean Steichen (steichjj@email.uc.edu); Jon Tyson (Jon.E.Tyson@uth.tmc.edu); Myriam Peralta (mperalta@peds.uab.edu); Rich Ehrenkranz (richard.ehrenkranz@yale.edu); Ricki Goldstein (golds005@mc.duke.edu); Robert Dillard; Roy Heyne; Susan Hintz; Yvonne Vaucher (Yvonne Vaucher); Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Walid Salhab (Walid Salhab)
Cc: Petrie, Carolyn; Newman, Jamie
Subject: Pulmonary follow up secondary to SUPPORT

Hi
Dr. Stevens has revised the questionnaires based on the comments from the FU Training meeting. Please review and send comments back by August 11 so this can get started.

Note from Dr. Stevens:
Attached are the revised questionnaires, including scripting that explains how the questions are to be asked and makes administering the questionnaire faster. Our telephone researchers trialed the questionnaires, it takes less than 10 minutes if the child has had only mild symptoms. A child with severe lung symptoms might take 20 minutes.

It is fine to administer the questionnaires in person. The Tucson Study administered them in person to some study participants.

I've also included a model of a Pulmonary Outcome Consent for patients already enrolled in SUPPORT. We'd like to include them in the Pulmonary Outcome data as well. We hope that each center will modify their primary SUPPORT consent to include consent for the Pulmonary Outcome Study (model sent previously).

Thanks
Rose

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

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NICHD, NIH
6100 Executive Blvd., Room 4B03B
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Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: nfiner@UCSD.Edu
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: fmartinez@UCSD.Edu
Subject: RE:
Date: Friday, August 05, 2005 11:51:15 AM

>Hi Rose
I sent the presentation to you and Wally and I will continue to work on it. I am still planning to get there. What day do I present - Monday or Tuesday?
Many thanks Rose
Neil

Neil
> I likely have the bulk of the slides you need as I have the various SUPPORT
> Powerpoint slides that have been developed over the last year. Let me know
> if you want me to go through them to develop a back-up presentation in the
> event you continue to have email issues.
>
>
> Don't worry about the meeting. My best to you and your family.
> Take care
> Rose
> -----Original Message-----
> From: nfiner@UCSD.Edu [mailto:nfiner@UCSD.Edu]
> Sent: Friday, August 05, 2005 7:02 AM
> To: wcarlo@peds.uab.edu
> Cc: Higgins, Rosemary (NIH/NICHD); fmartinez@UCSD.Edu
> Subject:
>
> Hi Wally
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> Its way too long, and at present I haven't found a connection that will
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>(b) (6) and I am uncertain as to what will happen.
> Thanks for coming to this meeting. I may have to leave after my presentation
>
> so that you could participate in any subsequent discussion.
> Neil

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Date: Friday, August 05, 2005 1:01:58 PM
Attachments: SUPPORT Trial Presentation Oxygen Meeting Aug 4 2005 (2).ppt

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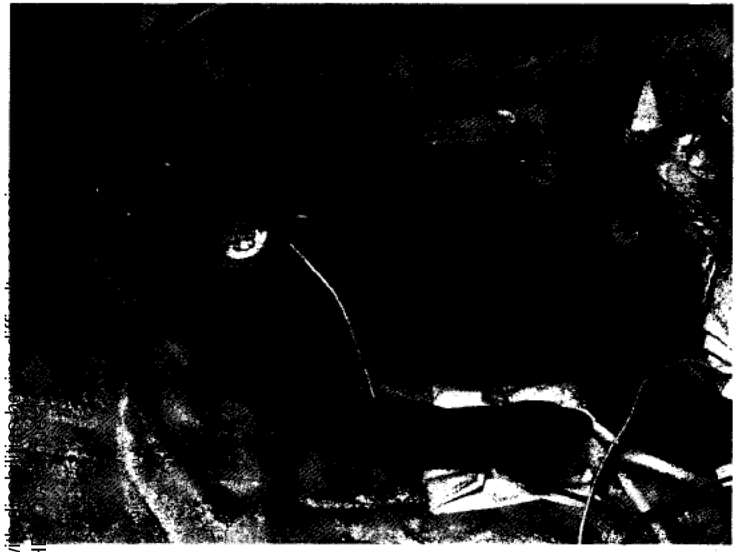
Dear Rose:

This is a shorter version (26 slides) given the time allotted for SUPPORT. Please feel free to make any changes.

Wally



SUPPORT TRIAL

Rationale
Evidence
Protocol

Next Trial : SUPPORT

- **Surfactant**
- **Positive airway pressure**
- **Pulse Oximetry**
- **Randomized**
- **Trial**

DR CPAP Trial NICHD Neonatal Network, Pediatrics, 2004;114:651-7

- **The Network (5 Centers) evaluated a prospective protocol which compared CPAP started at delivery versus the usual approach without DR CPAP**
- ***No infant could be intubated exclusively for surfactant in the DR***
- **All Infants were 28 weeks or less**
- **Intubated and received surfactant in NICU for minimal criteria:**

FiO2 > 0.3 to maintain SaO_2 > 90% or PaO_2 > 45 torr

Arterial $PaCO_2$ > 55-60 with pH < 7.25

Apnea requiring bag and mask ventilation

Patient Population
Means ± Standard Deviation

	CPAP N=55	Control N=48
Birth Weight	753 ± 196	799 ± 186
Gestation (weeks)	25 ± 1.3	25 ± 1.2
Apgar @ 1 min	4	4
Apgar @ 5 min	6	6
Apgar @ 10 min	6	6

Percent Intubated in DR by Gestational Age

Conclusions from DR- CPAP Trial

- ✓ ***All Infants < 24 weeks required DR Intubation for resuscitation!***
- ✓ **Early CPAP in the DR is a feasible intervention for infants ≥ 24 weeks**
- ✓ **It is possible to provide CPAP as a randomized intervention in the DR for the ELBW Infant**

SUPPORT Trial

- **Essentially 2 trials conducted simultaneously on the same population of ELBW infants**
- **A Factorial design which ensures that there will be an equal number of infants randomized to each of the 4 possible strategies**
- **Not prospectively powered to evaluate an interaction, but if a large interaction exists, it will be noted**

SUPPORT Trial

Randomized Intervention	Low SpO2 85% to 89%	High SpO2 91 to 95%
Early CPAP With Permissive Ventilation	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control with Prophylactic Surfactant	Control + Low SpO2	Control + High SpO2

PRIMARY HYPOTHESES

- **EARLY CPAP AND PERMISSIVE VENTILATORY STRATEGY WILL INCREASE SURVIVAL OF ELBW INFANTS WITHOUT BPD**

- **LOWER SpO2 (85-89%) WILL INCREASE SURVIVAL WITHOUT SEVERE ROP (THRESHOLD DISEASE OR REQUIRING SURGERY)**

Methods: CPAP/Permissive Ventilatory Strategy

- DR management guidelines
- Intubation criteria
- Extubation criteria
- Re-intubation criteria

SUPPORT Trial: Inclusion Criteria

- **Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate**
- **Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation**
- **Infants whose parents/legal guardians have provided consent for enrollment, or**
- **Infants without known major congenital malformations**

SUPPORT Trial: Exclusion Criteria

- Any infant transported to the center after delivery
- Infants whose parents/legal guardians refuse consent
- Infants born during a time when the research apparatus/study personnel are not available.
- Infants < 24 weeks 0 days or $\geq$ 28 weeks 0 days, completed weeks of gestation

Ventilation Criteria

- **In effect for 14 days for all study infants**
- **CPAP may be discontinued when in room air > 1 hour**
- **May be restarted at any time in either group**
- **Nasal SIMV to be used *only* after initial intubation**

Methods: Oxygen Saturation Strategy

Birth – Admit to NICU
Placed on Study Pulse Oximeter < 2 hours

SpO_2 – 85% - 89% **SpO_2 – 91% - 95%**

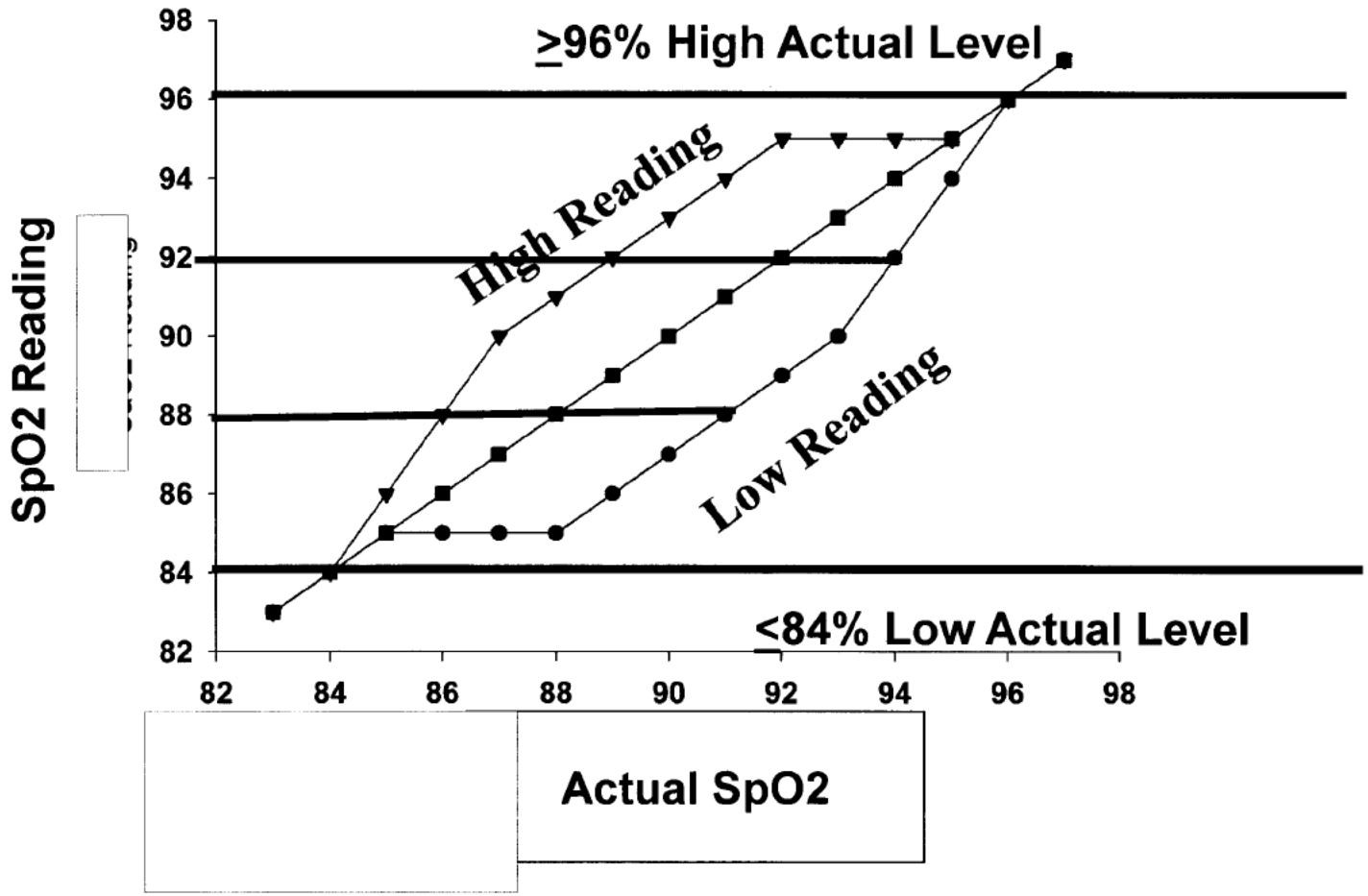
Maintain till off ventilatory support and oxygen

RANDOMIZATION	Displayed Target Range	Actual Range
Low SpO_2 range group	88-92%	85-89%
High SpO_2 range group	88-92%	91-95%

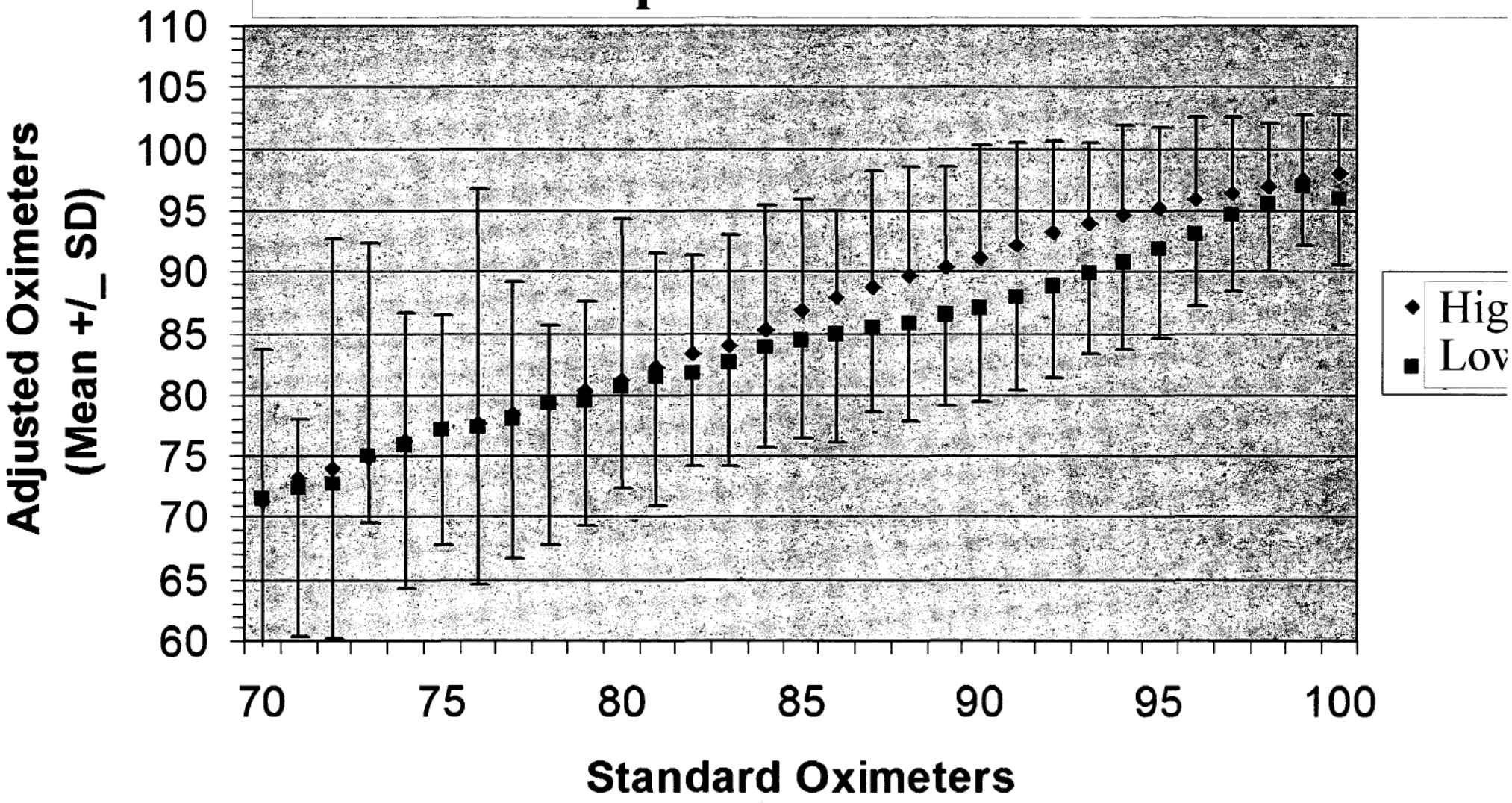
Pulse Oximetry Protocol

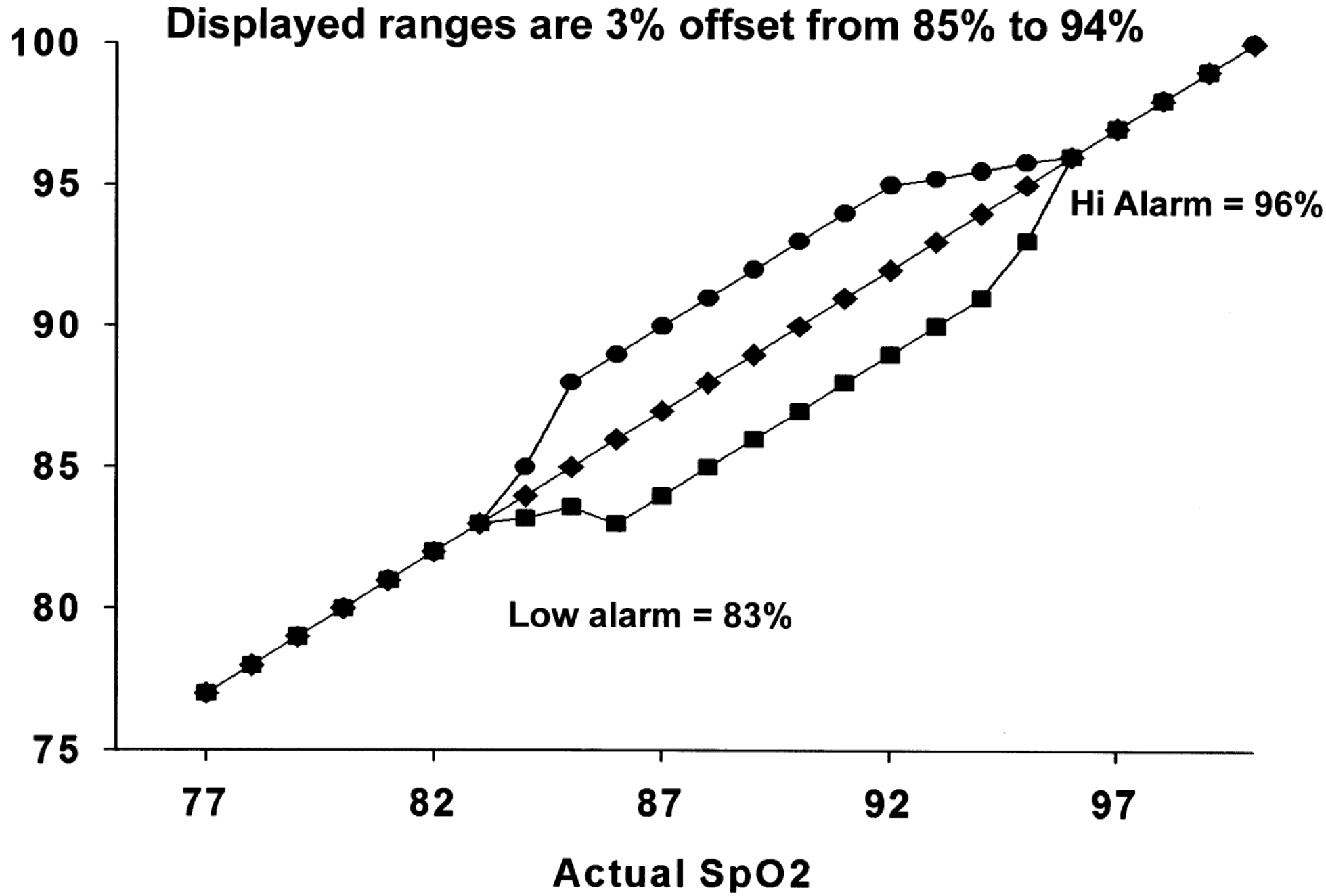
- **LOW RANGE: TARGET SpO2 85-89%**
- **HIGH RANGE: TARGET SpO2 91-95%**
- **STUDY PULSE OXIMETERS (PO) WILL BE SUPPLIED TO PARTICIPATING SITE**
- **STUDY PO'S READING NOT THE ACTUAL SpO2 for READINGS BETWEEN 85% TO 95% FOR BLINDING**

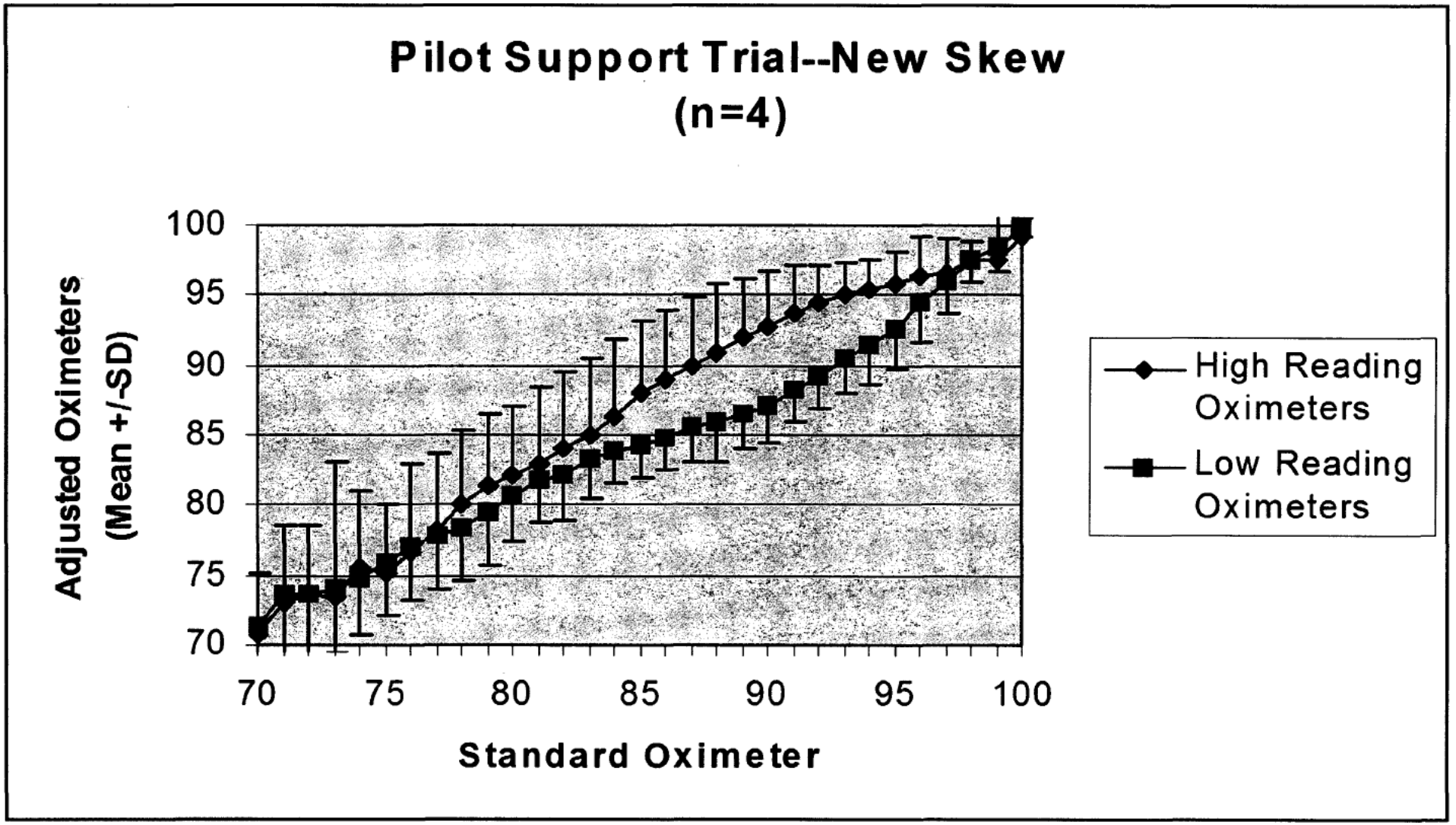
Plot of Actual versus Displayed SpO2



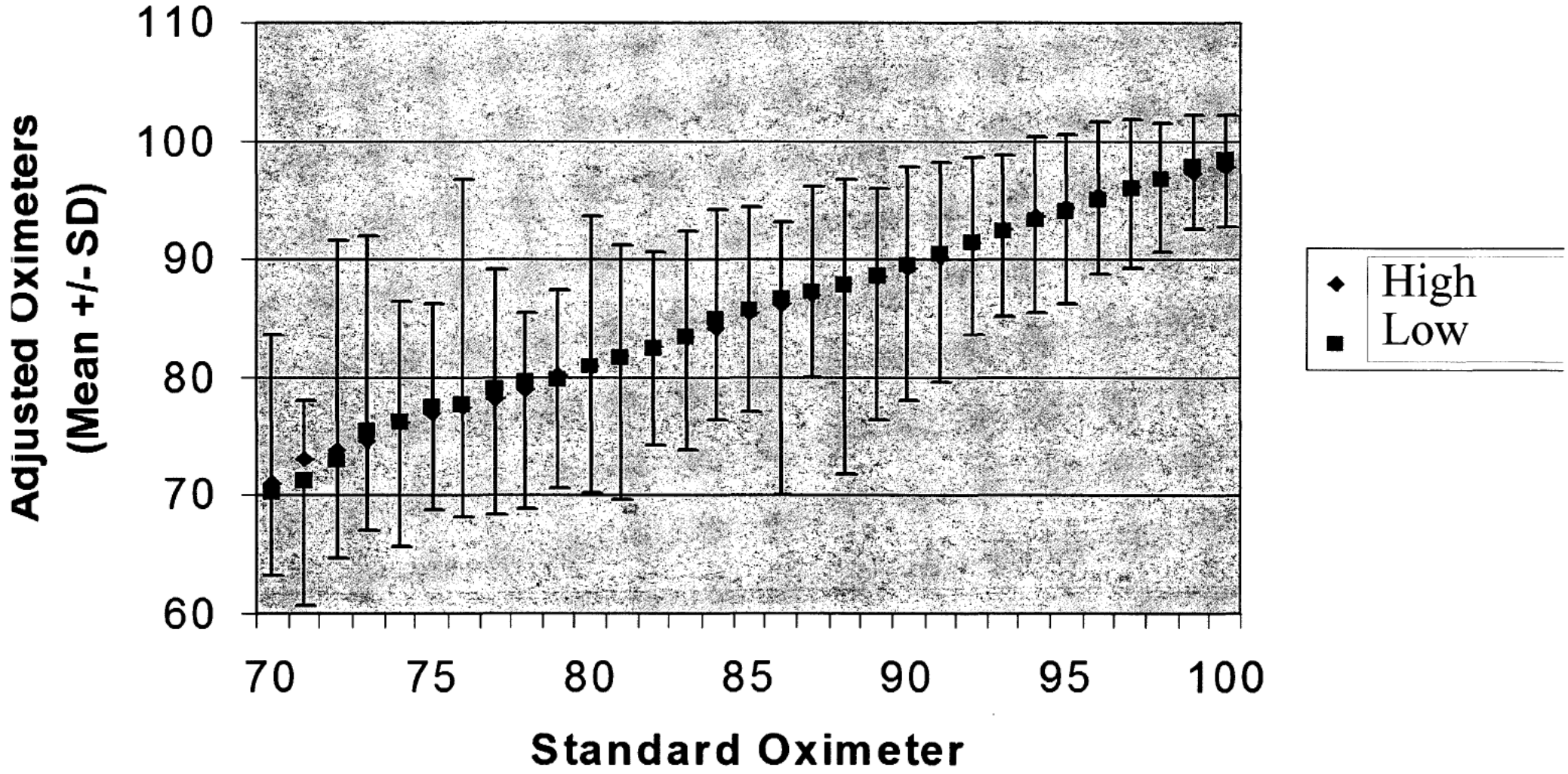
Comparison of High reading versus Low reading Oximeters Compared to a Standard Oximeter







Comparison of High reading versus Low reading Oximeters Corrected to Standard Readings



Pulse Oximetry Protocol

- **BOTH GROUPS WILL MAINTAIN DISPLAYED SATURATION AT 88-92%**
- **ALARMS FOR BOTH GROUPS WILL BE:**

  LOW – 85% HIGH - 95%

  (***Note Masimo alarms at actual limit set point, not one below*****)**
- **SPO2 READINGS BELOW 85% AND ABOVE 95% WILL BE ACTUAL, NOT ALTERED**

OXYGENATION PROTOCOL-CONT'D

- **STUDY PO WILL REMAIN WITH INFANT UNTIL OFF OXYGEN (for 3 days) or INFANT 36 WEEKS PCA whichever is sooner**
- **SpO2 FROM STUDY PO WILL BE DOWNLOADED TO RTI ONCE PER MONTH - every 2 WEEKS DURING STUDY**
- **This will contain 1 data point for SpO2 and heart rate for every 10 seconds of this 1 month interval**

Sample Size

- **Postulating a 10% difference in primary outcome a sample size of 1310 infants will provide for 80% power for the primary as well as NDI/Mortality (Secondary Outcome)**
- **This includes a 17% attrition factor**

SUPPORT – Current Status

- ✓ Enrollment now almost 100 infants
- ✓ We have downloaded about oximeters with 2-4 weeks of data
- ✓ We are within the large target zone of 85% to 95% approximately 55% to 60% of the time
- ✓ This is the zone with the altered SpO2 values

SUPPORT – Current Status

- Downloads better done every 14 days.
- After 28 days you start to loose data!!
- Few issues with respiratory support protocols
- Oximeters – some increased alarms
- This depends on type and settings of oximeters that were previously used.

Oximeter Information
SUPPORT Trial July 2005

- **At the present time based on the available downloads representing over 7000 hours of data we are in the range of 85% to 95% approximately 60% of the time for infants requiring oxygen, and 47% of the time for all infants irrespective of FiO2**

From: nfiner@UCSD.Edu
To: wcarlo@peds.uab.edu; wrich@UCSD.Edu; nfiner@UCSD.Edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; fmartinez@UCSD.Edu
Subject: Re:
Date: Friday, August 05, 2005 11:47:11 AM
Attachments: SUPPORT Trial Presentation Oxygen Meeting Aug 4 2005.ppt

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> Hi Wally
I'm sending this from Kinkos as I cannot get an email connection that will allow messages.
Here is the presentation. It is larger than I would present, and needs cutting.
Rose also asked that I talk a little about oximeters, and thus the last slides.
I am still going to try to come but will probably have to leave early, so having you there would be great.
Please modify as you see fit, and I will also try to improve.
Many thanks Wally
I'm sorry to have had to burden you with this, and I also think that you should be at this meeting. The oxygen side of this trial was your idea!!
Be well
Neil

Hi Rose: that would be helpful. I have a full talk on the subject but
> includes very few slides specific to SUPPORT.
> Wally
> Sent from my BlackBerry Wireless Handheld
>
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
> To: nfiner@UCSD.Edu <nfiner@UCSD.Edu>; Wally Carlo, M.D.
> <WCarlo@peds.uab.edu>
> CC: fmartinez@UCSD.Edu <fmartinez@UCSD.Edu>
> Sent: Fri Aug 05 06:21:38 2005
> Subject: RE:
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> Don't worry about the meeting. My best to you and your family.
> Take care
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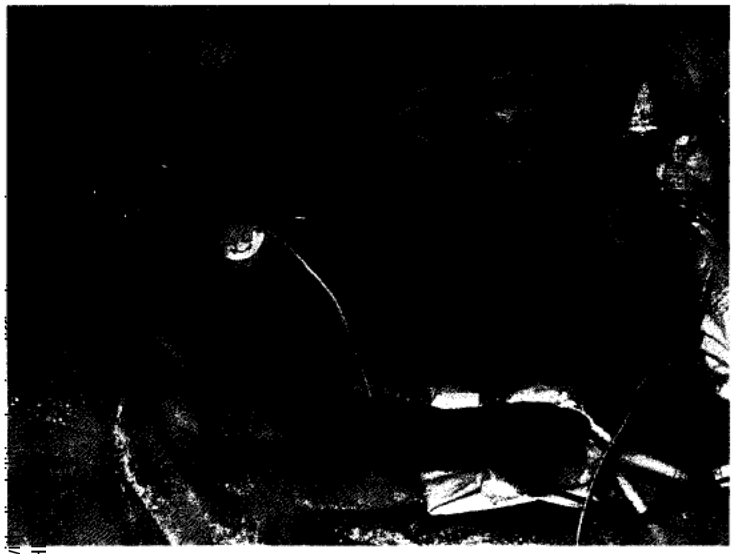

SUPPORT TRIAL

Rationale
Evidence
Protocol

Evidence for Efficacy of CPAP

- Gregory et al (NEJM 1971;284:1330) demonstrated that CPAP improved oxygenation in infants < 1500 gm with RDS
- Rhodes et al (Pediatr 1973;52:17) reported increase survival with face mask CPAP
- CPAP improves FRC and premature infants without adequate FRC are more likely to develop HMD (Upton et al, Arch Dis Child 1991;66:39)
- The use of CPAP decreases mortality in the presurfactant era (Ho et al Cochrane LibraryCLIB Issue #3 2002)

Evidence for Efficacy of CPAP: Population – European VLBW Cohort Studies

- Jonsson et al (Acta Pediatr 1997;419:4) reported experience from Stockholm from 1988 – 1993 and use of higher $PaCO_2$ 51% treated with early CPAP < 30 min usually, only 1/3 required intubation

✓ Almost all infants < 24 weeks required intubation

- Gitterman et al (Eur J Pediatr 1997;156:384) reported that CPAP usually within 15 min of birth, reduced the need for intubation mortality, and LOS
- Poets et al (Pediatr 1996;98:24) reported ⇩ ventilation, without increased BPD, IVH or PVL in Germany from 1992-1994

Evidence for Efficacy of CPAP: Last Pre-Surfactant Prospective Trial Han et al Early Human Dev 1987;15:21

- Compared early CPAP (up to 2hours after birth)
- ☹No maternal Antenatal Steroids
- ☹CPAP associated with worse oxygenation
- ✘ There is no Post-Surfactant Antenatal Steroid Era prospective RCT comparing DR/Early Surfactant to Surfactant
- ✘ Current Cochrane Review on Prophylactic CPAP concludes that a multicentered RCT comparing prophylactic CPAP with standardized care was needed! (Subramanian et al Cochrane Library Issue4 2003)

Origins of Chronic Lung Disease

- **Review of number of units demonstrated that the unit which used least ventilation, allowed permissive hypercarbia and used initial Nasal CPAP had lowest BPD rates (Columbia)**
- **This unit did not use muscle paralysis**
- **Recently reported low BPD rate = 3/81, (4.7%)**
- **50% survival without BPD for infants 500-750 gm**

Avery et al, Pediatr 1987:79:26

Interhospital Variation of Chronic Lung Disease:
Van Marter et al Pediatr 2000;105:1194

- **Compared early ventilatory practices for VLBW infants at 2 Boston Hospitals (341 infants) with Columbia (100 infants) born from 1991 to 1993**
- **They evaluated use of mechanical ventilation for days 1-3, and 4-7**

❁ ***CLD (O_2 at 36 weeks) was 4% (Babies) vs 22%(Boston)***

❁ **No differences in IVH, PVL, NEC, ROP, or mortality (9% vs 10%)**

Interhospital Variation of Chronic Lung Disease:
Van Marter et al Pediatr 2000;105:1194

Other practices: Babies vs Boston

- ✓ **Surfactant 10% vs 45% more often in CLD, 23% vs 65%**
- ✓ ***CPAP used primarily at Babies 63% vs 11%***
- ✓ ***Mechanical Ventilation as primary 29% vs 75%***
- ✓ **Infants with CLD more likely to receive Mechanical Ventilation 77% vs 42%**
- ✓ **Duration of Mechanical Ventilation 13 days vs 27 days**
- ✓ **$PaCO_2$ higher at Babies**

Mechanical Ventilation and Chronic Lung Disease:
Van Marter et al Pediatr 2000;105:1194

- **Overall Odds Ratio for the development of CLD was related to need for Mechanical Ventilation**
  - **on day of birth - OR = 13.4**
  - **Days 1 - 3 - OR = 9.6**
  - **Days 4 -7 -OR = 6.3**
  - **Maximum PIP of > 25 cmH_2O at birth, or > 20 cmH_2O at 1 -3 days increases risk for CLD**
  - ***Message: If you don't intubate, the babies do better!!!***
  - ***Oh by the way, this is all retrospective information!!!***

Mechanical Ventilation and Chronic Lung Disease:

Serenius et al Acta Paediatrica. 2004; 93(8):1090-1097

- **Other studies have reported association between duration of ventilation and BPD/CLD**
- **BPD was associated with duration of mechanical ventilation (OR 2.71 per 1-wk increment in duration; 95% CI 1.76-4.18)**
- **Other morbidities associated with ventilation**
- **Severe IVH or PVL was associated with duration of mechanical ventilation (OR 1.53 per 1-wk increment in duration; 95% CI 1.01-2.33)**

Nasal CPAP and Early Surfactant for < 30 wk Infants:

Verder et al, Pediatr 1999;103(2).

- 11 Neonatal Units in Denmark from April 1995 to Jan 1997
- Previous study (NEJM 1994;331:1051) showed benefit for early CPAP (not DR) followed by intub + Surf + extubation
- Infants < 30 wks, + RDS, a/APO_2 was .35-.22 on CPAP $\geq$ 6 cmH_2O
- <u>Treated with early CPAP and given Surfactant</u>
- Randomized to :early Curosurf vs later when a/APO_2 < .21-.15
- Infants intubated for Curosurf 2.5ml/kg in 2 doses,

  then extubated, usually within 10 minutes!!!

Verder et al, Pediatr 1999;103(2).

Results: BW=950gm vs 935, Gest=27 vs 28, Nasal CPAP started at median of 17 minutes

➔Randomization at 4.3 hours

➔Early Rx rec'd Surfactant at 5.2 hrs vs 9.9 hrs for late group

➔Only 4 infants could not be extubated after Surfactant instillation

➔MVent/Death = 21% vs 63%, p=0.0013 by logistic regression

➔Death = 9% for Early Rx vs 26% for late Rx

Early CPAP and Surfactant
Verder et al, *Pediatr 1999;103(2).*

- **This was a trial of early not DR CPAP**
- **Also tested surfactant at approximately 4 hours – this is neither prophylactic nor early**
- **Compared earlier vs later rescue surfactant**
- **Could initially extubate all but 4 infants, 2 in each group**
- **6 early and 12 late treated infants required ventilation**

Evidence for Efficacy of DR CPAP: Lindner et al, Pediatr 1999;103:961

- Evaluated prolonged inflation (20-25 cm H2O for 15 secs) followed by CPAP
- Accepted high PaCO2 >70 torr and FiO2 > .6
- Reported a reduction in intubation from 84% in 1994 to 40% in 1996
- No difference in mortality, IVH,BPD and no airleaks on admission to NICU

Sustained Inflations: Do they work?

Lindner et al, Acta Pediatr 2005;94:303

- ✓ **Compared sustained pressure-controlled inflation (15 s) or to intermittent mandatory ventilation @ 60 bpm, given by a nasopharyngeal tube**
- ✓ **The inflation pressure or peak inspiratory pressure increased stepwise (20-25-30 cm H2O) according to the response of heart rate and oxygenation.**
- ✓ **Endotracheal intubation and mechanical ventilation occurred in 61% and 70%**
- ✘ **The rates of mortality severe IVH and CLD not different**

Evidence for Early CPAP: Recent Cohort Studies

- De Klerk and de Klerk (J Pediatr Child Health) 2001;37:161) used CPAP within 10 minutes of birth for infants 1000-1500 gm
- Reported decreased intubation, surfactant use, and ventilation duration and oxygen at 28 days.

Early CPAP in the ELBW Infant

Narendran et al, J Perinatol 2003;23:195

- **Evaluated infants 401-1000 gm and compared historical cohort N=92, with Bubble CPAP initiated in DR, N=79**
- **Gest = 26 weeks, BW = 760 gm**
- **Reported decreases for:**

✓ **DR Intubations - 60% versus 32%**

✓ **Duration of Mech Ventilation – 28 versus 13**

✓ **Use of Post Natal Steroids – 42% versus 14%**

Evidence for Early CPAP:

Thomson et al, Ped Res 2002;45:321A

- **Thomson et al, 237 27-29 week infants - 4 arms – CPAP + Rescue surf, Surf followed by Surf, Early IPPV + Surf, Conventional Management**
- **CPAP began < 6 hours in 76-79% - not DR, not really early**
- ✗ **No differences for CLD**
- **These are most recent studies**

Current Evidence for Early CPAP:

Sandri et al, Arch Dis Child 2004;89:F394-98

- **230 infants 28 to 31 weeks**
- **Randomized to early CPAP < 30 min Mean age = 19min**

  or
- **Rescue CPAP – required FiO2 > .40 for > 30 min for SpO2 93% to 96%**
- **CPAP given with a flow driver 4-6 cm H20**
- **All infants who required > .40 FiO2 on CPAP, and had X-ray compatible with RDS were intubated for surfactant, and then extubated**
- **MVent for FiO2>.40, PaCO2 > 70 with pH < 7.2,or Apnea**

Current Evidence for Early CPAP:

Sandri et al, Arch Dis Child 2004;89:F394-98

- ✓ **Well matched, 115 /gp GA = 30 wks, BW = 1350gm**
- ✓ **Need for Surfactant = 22.6% vs 21.7%**
- ✓ **Need for MVent = 12.2% in both groups**
- ✓ **66/115 Rescue CPAP actually received CPAP at 108 min**
- ✓ **CLD rates (Oxygen at 36 wks) 1.7% vs 0.9%**

- ✓ **SUPPORT will enroll only infants < 28 weeks – None of the above!!**

Early CPAP vs Mechanical Ventilation Recent Trials

- In a study of infants < 28 wks in France,
- 40 received DR CPAP, 20 (50%) subsequently intubated (Boubred et al PAS 2004)
- Dani et al, (Pediatr 2004;113:E560)
- 27 infants < 6 hrs age, < 30 wks on CPAP (started at 35 min) and FiO2 > .3
- Intubated for curosurf, then randomized to CPAP within 5 min (13) vs MVent (14)
- CPAP infants req'd less ventil, oxygen and surfactant and had shorter LOS.

Early CPAP as Support for ELBW "Columbia Approach, A Sirens Song?"

- **We have been seduced into believing that we can avoid intubating ELBW infants by observations presented by many about a few who never published anything prospective about their own practice!!**
- **Much speculation that infants < 700 gm can be managed without intubation**
- **This approach has *Never* been shown to produce good outcomes by any prospective trial**
- **Most current studies have excluded infants < 25 weeks**

DR CPAP Trial NICHD Neonatal Network, Pediatrics, 2004;114:651-7

- **The Network (5 Centers) evaluated a prospective protocol which compared CPAP started at delivery versus the usual approach without DR CPAP**
- ***No infant could be intubated exclusively for surfactant in the DR***
- **All Infants were 28 weeks or less**
- **Intubated and received surfactant in NICU for minimal criteria:**

FiO2 > 0.3 to maintain SaO_2 > 90% or PaO_2 > 45 torr

Arterial $PaCO_2$ > 55-60 with pH < 7.25

Apnea requiring bag and mask ventilation

Patient Population
Means ± Standard Deviation

	CPAP N=55	Control N=48
Birth Weight	753 ± 196	799 ± 186
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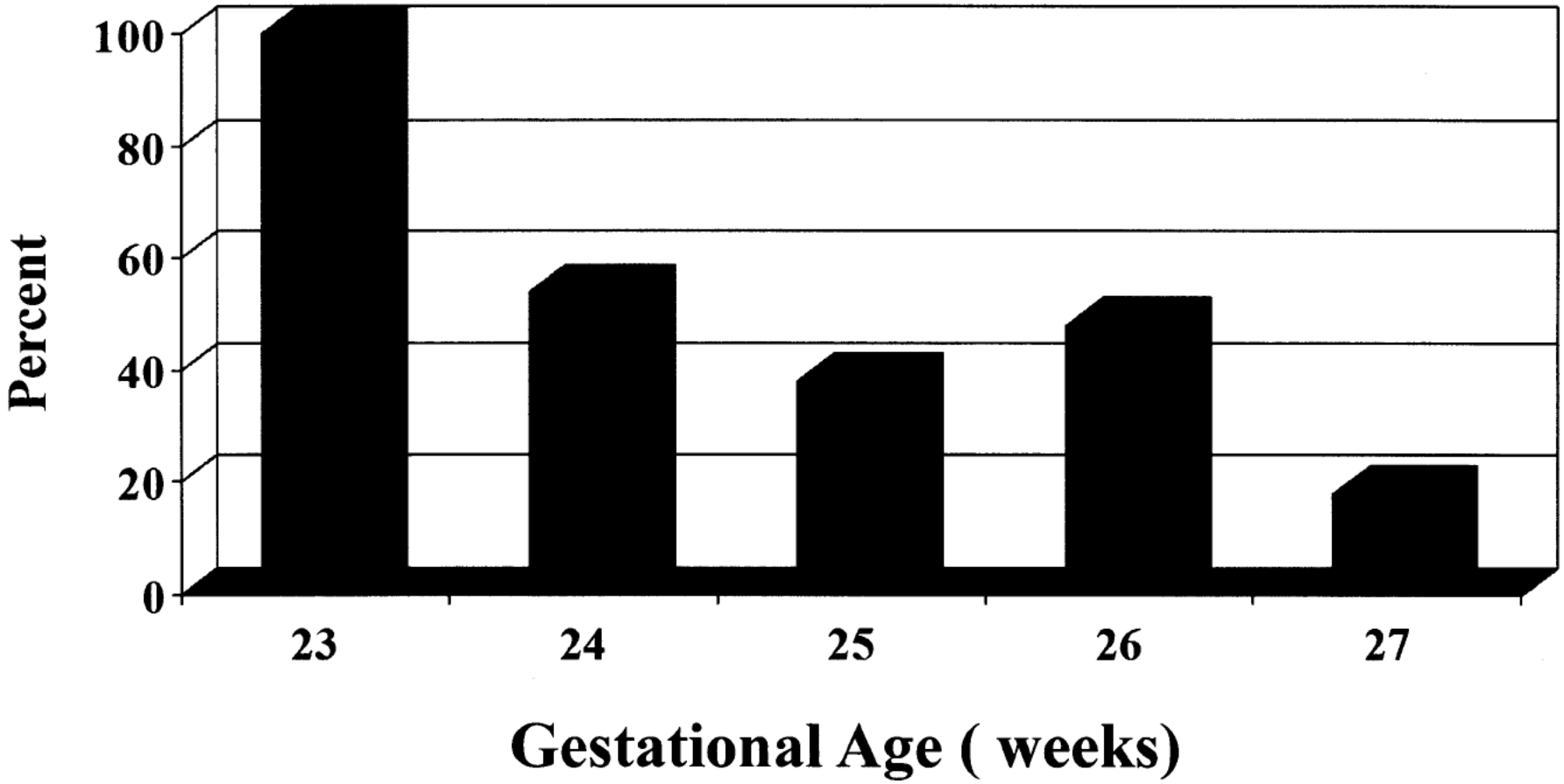
Apgar @ 10 min	6	6

Percent Intubated in DR by Gestational Age



Conclusions from DR- CPAP Trial

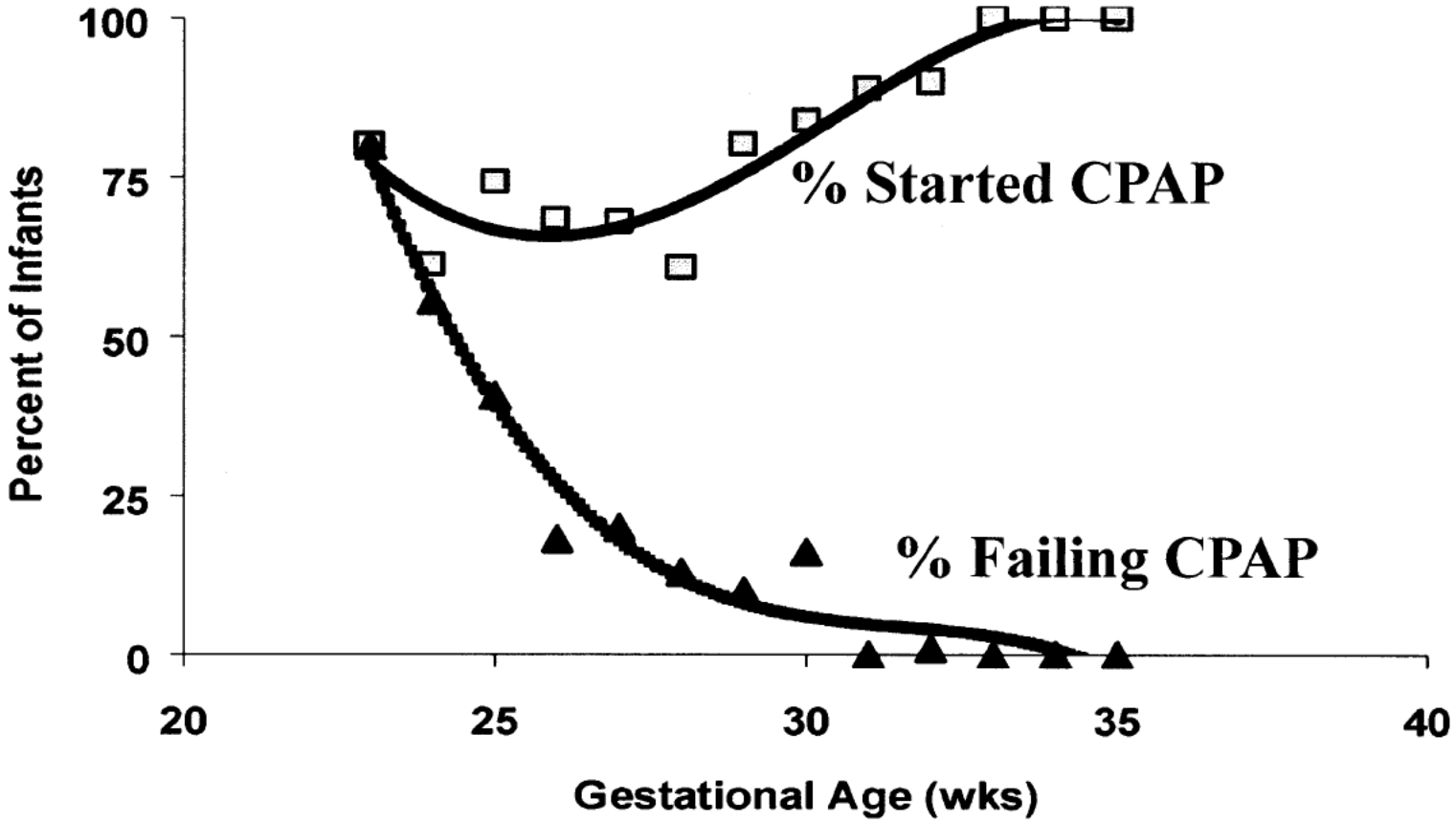
- ✓ ***All Infants < 24 weeks required DR Intubation for resuscitation!***
- ✓ **Early CPAP in the DR is a feasible intervention for infants > 24 weeks and > 500 gm**
- ✓ **It is possible to provide CPAP as a randomized intervention in the DR for the ELBW Infant**

DR use of CPAP for ELBW Infant

Aly et al, Pediatrics. 2005; 115(6):1660-1665

- **Retrospectively evaluated outcomes of VLBW infants treated with early CPAP**
- **Reported that only 10% of infants < 24 weeks could be managed with CPAP alone for > 48 hours**
- **At 25 weeks this improved to 45%**

ENCPAP implementation and failure rates at different GAs



Aly, H. et al. Pediatrics 2005;115:1660-1665

PEDIATRICS

CPAP vs Mechanical Ventilation from Birth Beneficial Effects: Animal Studies

- **CPAP from birth in preterm lambs produces gas exchange similar to or better than mechanical ventilation for 72 hours (Null et al, PAS May 2004)**
- **Preterm lambs treated with CPAP from birth at 2 hours had lungs with greater volumes and lesser neutrophils and hydrogen peroxide than lambs ventilated from birth (Jobe et al, Ped Res 2002:52:387)**

Potential Benefits of Early CPAP Avoid Volutrauma and Hypocarbia

Bjorklund et al, Pediatric Research. 1997 ;42(3):

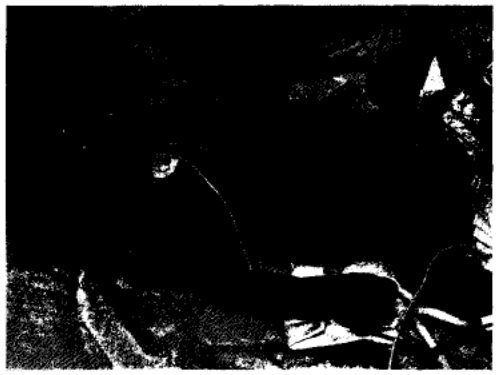
- ✓ **Five pairs of lamb siblings were delivered by cesarean section at 127-128 d of gestation. One lamb in each pair was randomly selected to receive six manual inflations of 35-40 mL/kg prior to surfactant Rx**
- ✘ **Large breaths inhibited surfactant induced increase in compliance and lung volume, and caused more lung injury**
- ✘ **"a few inflations with volumes that are probably harmless in other circumstances might, when forced into the surfactant-deficient lung immediately at birth, compromise the effect of subsequent surfactant rescue treatment."**

What Type of CPAP- Does it Matter?

- **No data to date suggests that one form of CPAP is clinically better than another – Bubble vs Conventional**
- **Variable flow CPAP associated with lower work of breathing and improved compliance, but no effect on FRC and no clinical advantages detected (Pandit et al, Pediatr 2001, Courtney et al, Pediatr 2001, PAS 2004, Stefanscu et al Pediatr 2003, McEvoy et al PAS 2004)**
- **High Frequency CPAP used in 132 day old lambs for 72 hours compared with CMV resulted in better oxygenation over time, with no significant differences in $PaCO_2$ (Null et al, PAS May 2004)**

How Much CPAP??
Animal and Infant Studies

- ✓ CPAP of 8 cmH_2O vs 5 cm H_2O for 6 hours produces better oxygenation than Mechanical ventilation and improves fluid clearance (Mulrooney et al PAS, May 2004)
- ✓ Increasing CPAP improves oxygenation but > 8 cm H_2O may increase air leaks (Probyn et al, Ped Res In Press)
- ✓ Increasing CPAP increases lung volume in preterms, more so with variable flow CPAP (Pandit et al Pediatr 2001)



Most evidence for the beneficial effects of CPAP were described before the introduction of Surfactant

Little is known about the interaction between prophylactic or rescue CPAP and prophylactic or rescue Surfactant

Surfactant versus CPAP

- **The current dilemma is that there is an increasing interest in using early CPAP but the best available evidence indicates that intubation and prophylactic/early surfactant produces the best outcomes**
- **Unfortunately, there are no prospective randomized trials comparing these approaches, especially in the ELBW Infant!!**

CPAP Physiologic Effects May Offset Surfactant Benefit!!

- ☑ Decreases the work of breathing,
- ☑ Establishes and maintain an adequate functional residual capacity,
- ☑ Stabilizes air space, and promotes the release of surfactant stores.
- ☑ Avoiding endotracheal intubation is of benefit for mucociliary transport and humidification of inspired air, as well as decreasing the risk of airway damage and secondary infection and the occurrence of lung barotrauma and volutrauma secondary to MV

Comparison of Early CPAP to Surfactant: Current Studies

- ✓ **COIN trial – enrolling spontaneously breathing infants of ≥ 25 weeks to 28 6/7ths weeks – DR CPAP (single nasal prong) vs IPPV +Surfactant**
- ✓ **VON - 3 arms, Early Surf + Vent, Early Surf + Early extubation, Early CPAP + Selective Intubation – All infants > 25 weeks Gestation**

Comparison of Early Surfactant with CPAP

- ✘ No study to date has addressed the most vulnerable population of infants of 24 weeks where survival is now > 50%
- ✓ NICHD Neonatal Network *SUPPORT* trial will compare Prophylactic/Early Surfactant (< 1 hour) to CPAP initiated at birth
- ✓ 2 Strata – 24 to 25 6/7wks and 26 to 27 6/7 wks
- ✓ Will evaluate Neonatal Survival without ROP, BPD and Neurodevelopmental Impairment at 2 years

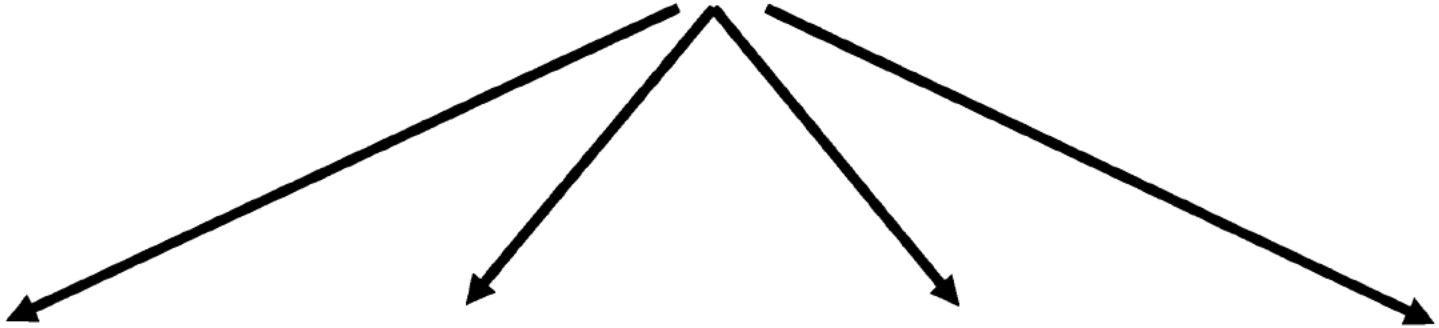
Next Trial : SUPPORT

- **Surfactant**
- **Positive airway pressure**
- **Pulse Oximetry**
- **Randomized**
- **Trial**

SUPPORT Trial

- **Essentially 2 trials conducted simultaneously on the same population of ELBW infants**
- **A Factorial design which ensures that there will be an equal number of infants randomized to each of the 4 possible strategies**
- **Not prospectively powered to evaluate an interaction, but if a large interaction exists, it will be noted**

Overall Study Design



CPAP + Lo SaO2 | CPAP + Hi SaO2 | SOC + Hi SaO2 | SOC + Lo SaO2

We hypothesize that that the use of CPAP and a permissive ventilatory strategy begun in the delivery room in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without CLD at 36 weeks.

We hypothesize that the use of a lower SaO2 range (85% to 89%) will result in an increase in survival without the occurrence of ROP or occurrence of threshold ROP and/or the need for surgical intervention.

We hypothesize that the combination of early CPAP and a permissive ventilator strategy with a lower SaO2 range will result in increased long term survival without severe developmental impairment as assessed at 18-22 months corrected age.

SUPPORT Trial

Randomized Intervention	Low SpO2 85% to 89%	High SpO2 91 to 95%
Early CPAP With Permissive Ventilation	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control with Prophylactic Surfactant	Control + Low SpO2	Control + High SpO2

PRIMARY HYPOTHESIS

- **EARLY CPAP AND PERMISSIVE VENTILATORY STRATEGY WILL INCREASE SURVIVAL OF ELBW INFANTS WITHOUT BPD**

- **LOWER SpO2 (85-89%) WILL INCREASE SURVIVAL WITHOUT SEVERE ROP (THRESHOLD DISEASE OR REQUIRING SURGERY)**

Methods: CPAP/Permissive Ventilatory Strategy

- DR management guidelines
- Intubation criteria
- Extubation criteria
- Re-intubation criteria

SUPPORT Trial: Inclusion Criteria

- **Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate**
- **Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation**
- **Infants whose parents/legal guardians have provided consent for enrollment, or**
- **Infants without known major congenital malformations**

SUPPORT Trial: Exclusion Criteria

- Any infant transported to the center after delivery
- Infants whose parents/legal guardians refuse consent
- Infants born during a time when the research apparatus/study personnel are not available.
- Infants < 24 weeks 0 days or $\geq$ 28 weeks 0 days, completed weeks of gestation

SUPPORT - Ventilation Arm

- **Will test the use of early CPAP started in the delivery area combined with a permissive ventilator strategy compared to a standard of care approach involving prophylactic/early surfactant within 1 hour of delivery**

SUPPORT TRIAL

Ventilation Strategies - First Hour

Treatment Arm

DR CPAP

Control Arm

Intubation and Early Surfactant < 1 hr

SUPPORT TRIAL
Ventilation Strategies - NICU

Treatment CPAP Arm

Intubation Criteria – Intubation is *Not Mandatory* for CPAP infants

May intubate CPAP Infants for Any of

FiO_2 >.50 for $SpO_2 \leq 88\%$
$PaCO_2$ > 65 torr
Hemodynamic instability

SUPPORT TRIAL
Extubation for TREATMENT - CPAP Infants

Must *Extubate* within 24 hrs of all criteria being met

$PaCO_2$ < 65 torr and pH > 7.20
SpO2 ≥ 88% with FiO2 ≤ .50
MAP < 10 cmH_20 Rate ≤ 20 bpm
Amp < 2X MAP if on HFV
Hemodynamically Stable

Criteria apply for first 14 days of life

SUPPORT TRIAL
Re-Intubation for TREATMENT - CPAP Infants

May *Intubate* within 24 hrs of all criteria being met

- **$PaCO_2 < 65$ torr and pH > 7.20**
- **$SpO_2 \geq 88\%$ with $FiO_2 \leq .50$**
- **Hemodynamic Instability**

Criteria apply for first 14 days of life

CPAP Arm
Reintubation - Extubation

- **Once a CPAP infant has been intubated for the *third time*, that infant's subsequent management will follow unit standard of care**
- **We do not want to create artificial/protocol driven cycles of intubation/extubation**
- **For such infants subsequent extubation will be at the attending physician's discretion**

SUPPORT TRIAL
Ventilation Strategies - NICU

Control Surfactant Arm

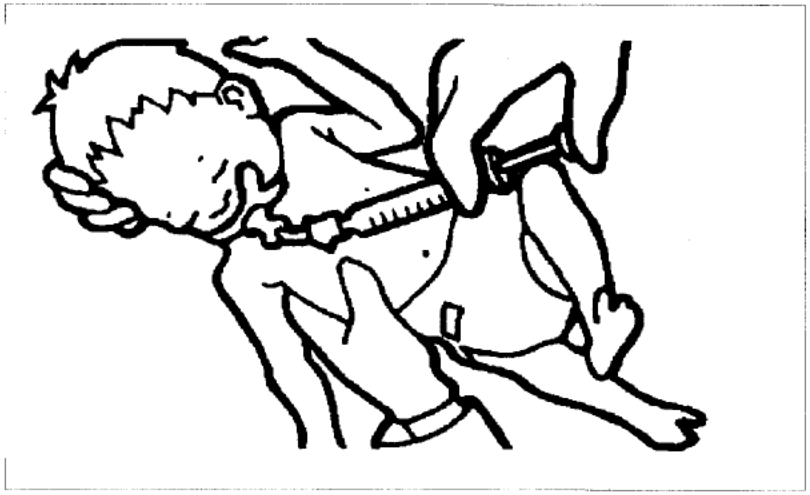
Will remain Intubated until they meet the following Criteria
Extubation can take place within 24 hrs of criteria

- **FiO2 < .35 for SpO2 ≥ 88%**

pH > 7.30 and PaCO2 < 50 torr
MAP < 8 cm H_2O, Rate ≤ 20 bpm,
If HiFi, Amplitude < 2X MAP
Hemodynamically stable
No significant PDA

SUPPORT TRIAL

Re-intubation Criteria - Control - Surfactant



Once extubated, a Control – Surfactant infant may be re-intubated following current Standard of Care

SUPPORT - Ventilation Arm

- **Treatment infants will be forced to early extubation attempt at higher ventilation settings**
- **Control infants will be extubated at more conventional settings**
- **Spontaneous extubation will not require mandatory re-intubation, unless intubation criteria are met.**
- **Intubation may be performed at any time for apnea, sepsis, shock or surgery**

Ventilation Criteria

- **In effect for 14 days for all study infants**
- **CPAP may be discontinued when in room air > 1 hour**
- **May be restarted at any time in either group**
- **Nasal SIMV to be used *only* after initial intubation**

Oximetry Arm: Justification

- **There are major questions regarding the appropriate level of oxygen exposure during the acute management of the ELBW infant**
- **Retrospective data suggests that infants maintained SpO2 values of 88% to 98% had 4 times the incidence of ROP as infants managed with lower SpO2 values - as low as 70% (Tin et al, Arch Dis Child Fetal Neonatal Ed. 2001 Mar; 84(2):F106-10.)**

Oximetry Arm: Justification

- **Chow et al at Cedars in LA adopted an approach which involved a number of interventions including less oxygen during resuscitation, and a subsequent SpO2 range of 85% to 93% for infants < 32**
- **They reported a significant decrease in ROP Grades 3 to 4 from 12.5% in 1997 to 2.5% in 2001 and ROP laser treatment from 4.5% in 1997 to 0% in the last 3 years of this intervention (Pediatr 2003; 111(2):339-345)**

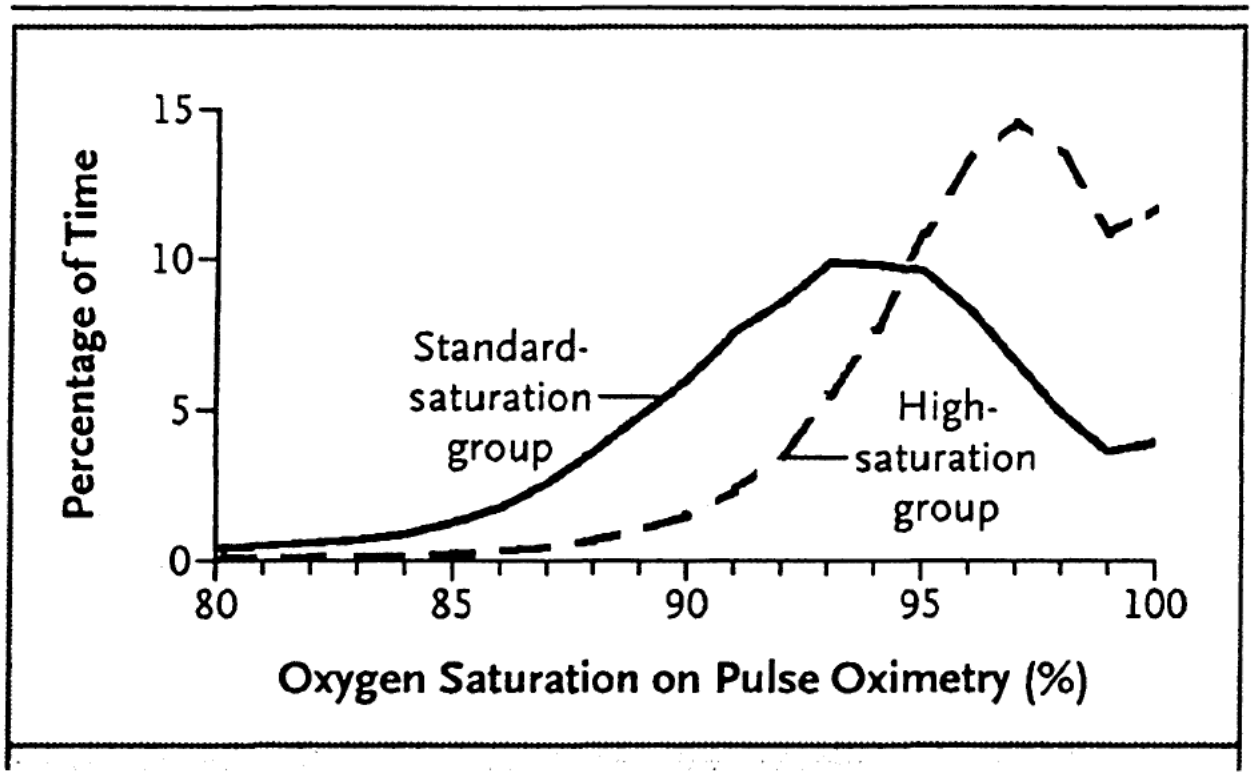
Oximetry Arm

- No other trial has prospectively evaluated the SpO2 level from birth onwards
- BOOST and STOP-ROP began when infants were $\geq$ 32 weeks of age
- They used ranges of 91-94% and 95-98%
- They both reported more pulmonary morbidity and a longer need for oxygen in their high saturation group where SpO2 was $\geq$ 95%
- Our study will keep SpO2 $\leq$ 95% for both groups

BOOST Trial
Askie et al, NEJM 2003;349;959

- **BOOST used a 2% adjustment in the SpO2 reading**
- **Low range infants read 2% lower than actual and hi range infants read 2% higher throughout the entire SpO2 range.**
- **Target range was 93 – 96%**

SpO2 from BOOST Trial
Askie et al NEJM 2003;349:959-67



Methods: Oxygen Saturation Strategy

Birth – Admit to NICU
Placed on Study Pulse Oximeter < 2 hours

SpO_2 – 85% - 89% **SpO_2 – 91% - 95%**

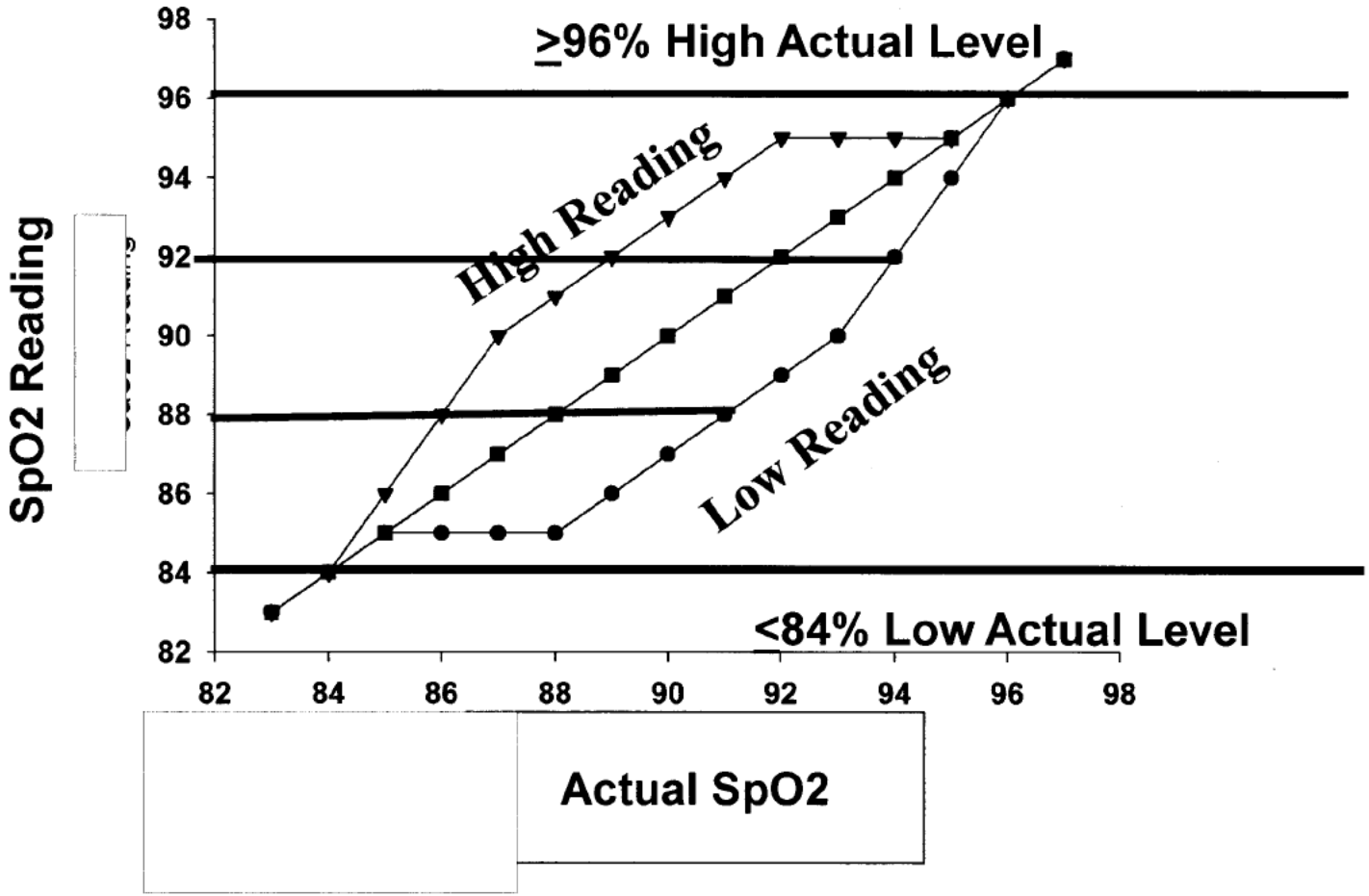
Maintain till off ventilatory support and oxygen

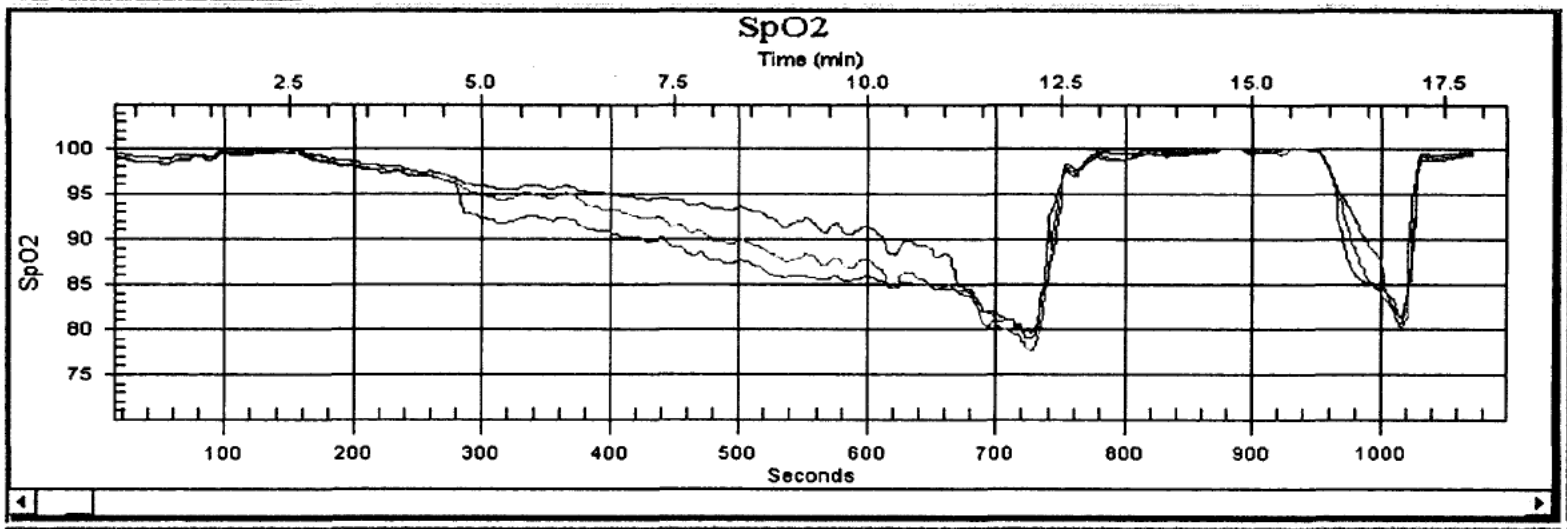
RANDOMIZATION	Displayed Target Range	Actual Range
Low SpO_2 range group	88-92%	85-89%
High SpO_2 range group	88-92%	91-95%

Pulse Oximetry Protocol

- **LOW RANGE: TARGET SpO2 85-89%**
- **HIGH RANGE: TARGET SpO2 91-95%**
- **STUDY PULSE OXIMETERS (PO) WILL BE SUPPLIED TO PARTICIPATING SITE**
- **STUDY PO'S READING NOT THE ACTUAL SpO2 for READINGS BETWEEN 85% TO 95% FOR BLINDING**

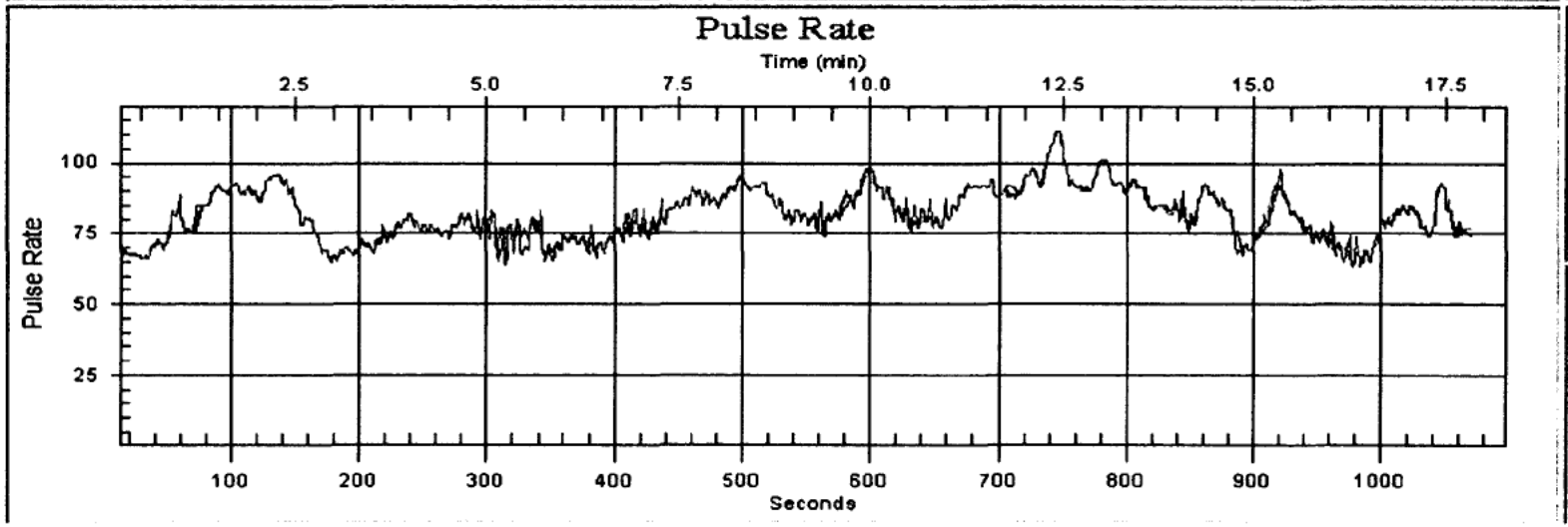
Plot of Actual versus Displayed SpO2



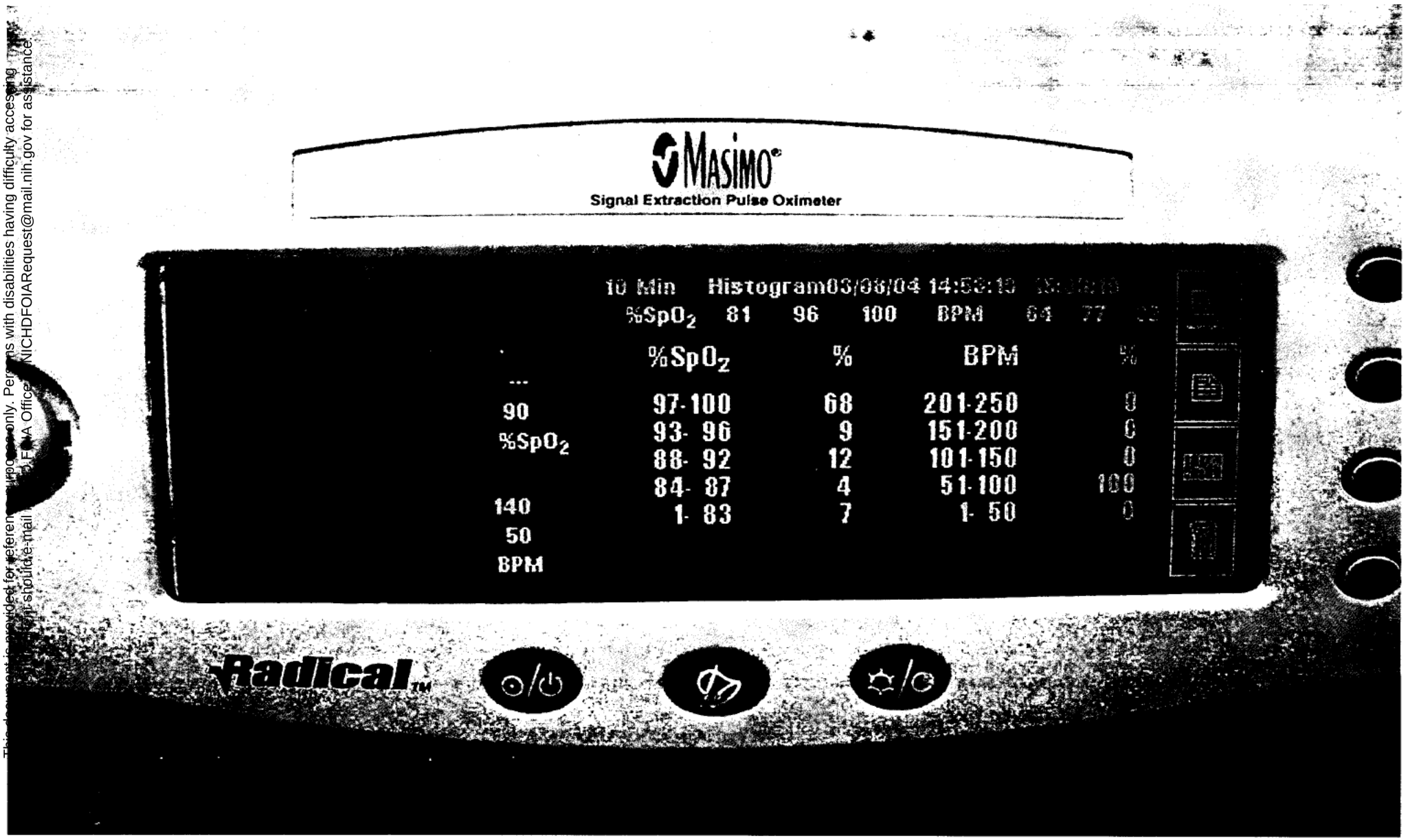


SpO2 Instruments:
REF Radical SpO2
Low Group : SpO2
High Group : SpO2

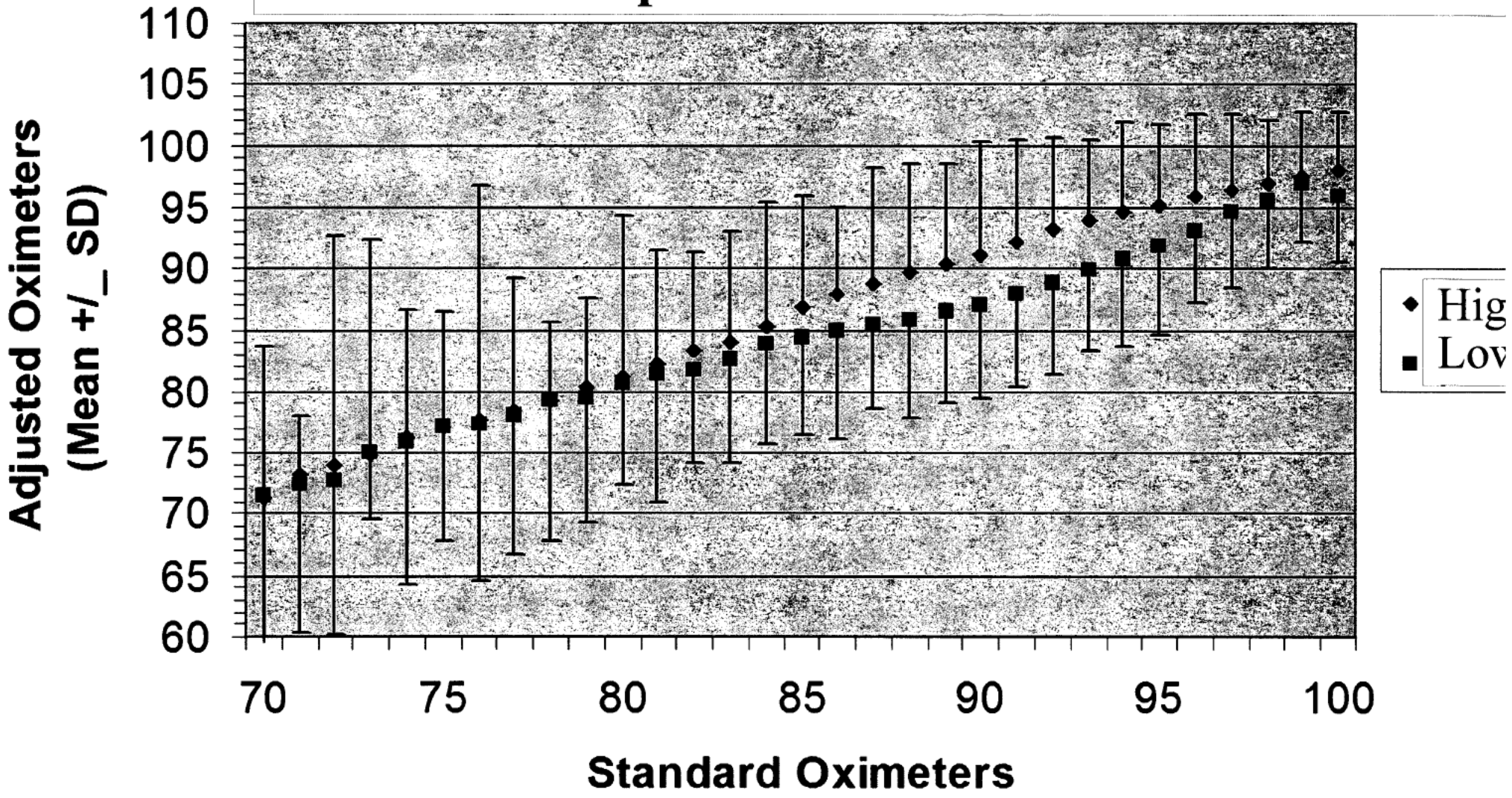
SpO2 Comment:

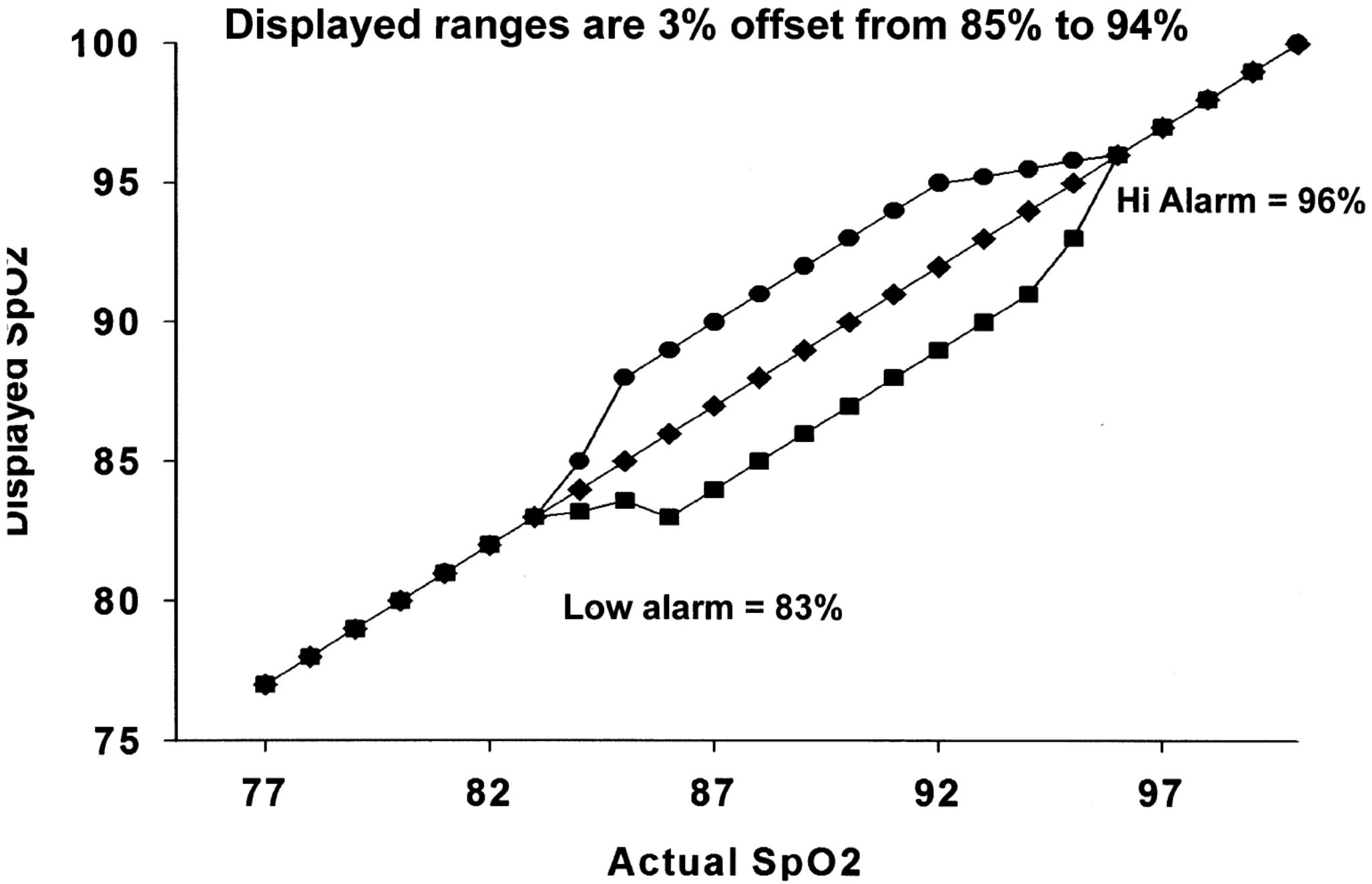


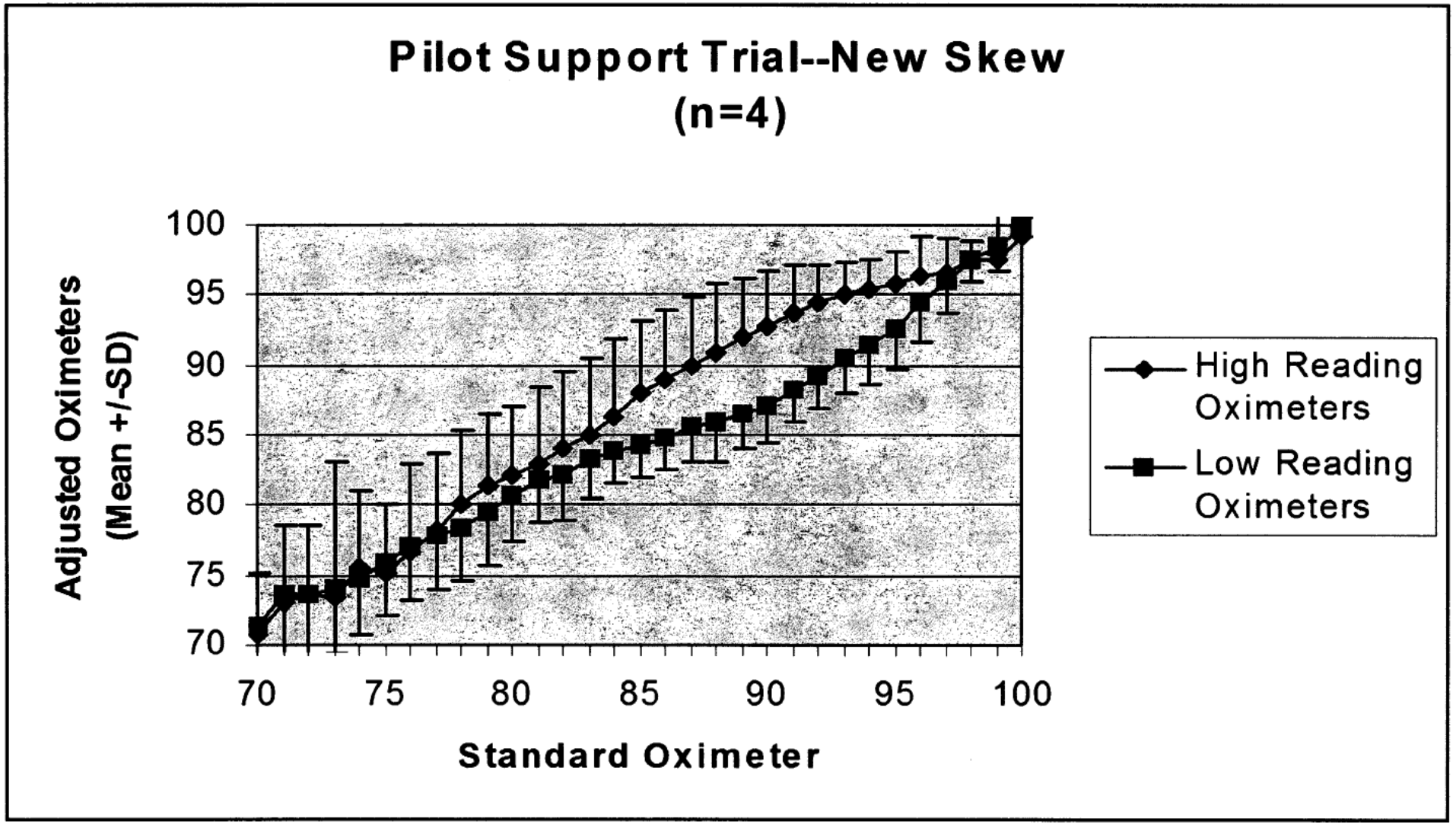
Pulse Rate Instrument
REF Radical PR
Low Group : PR
High Group : PR



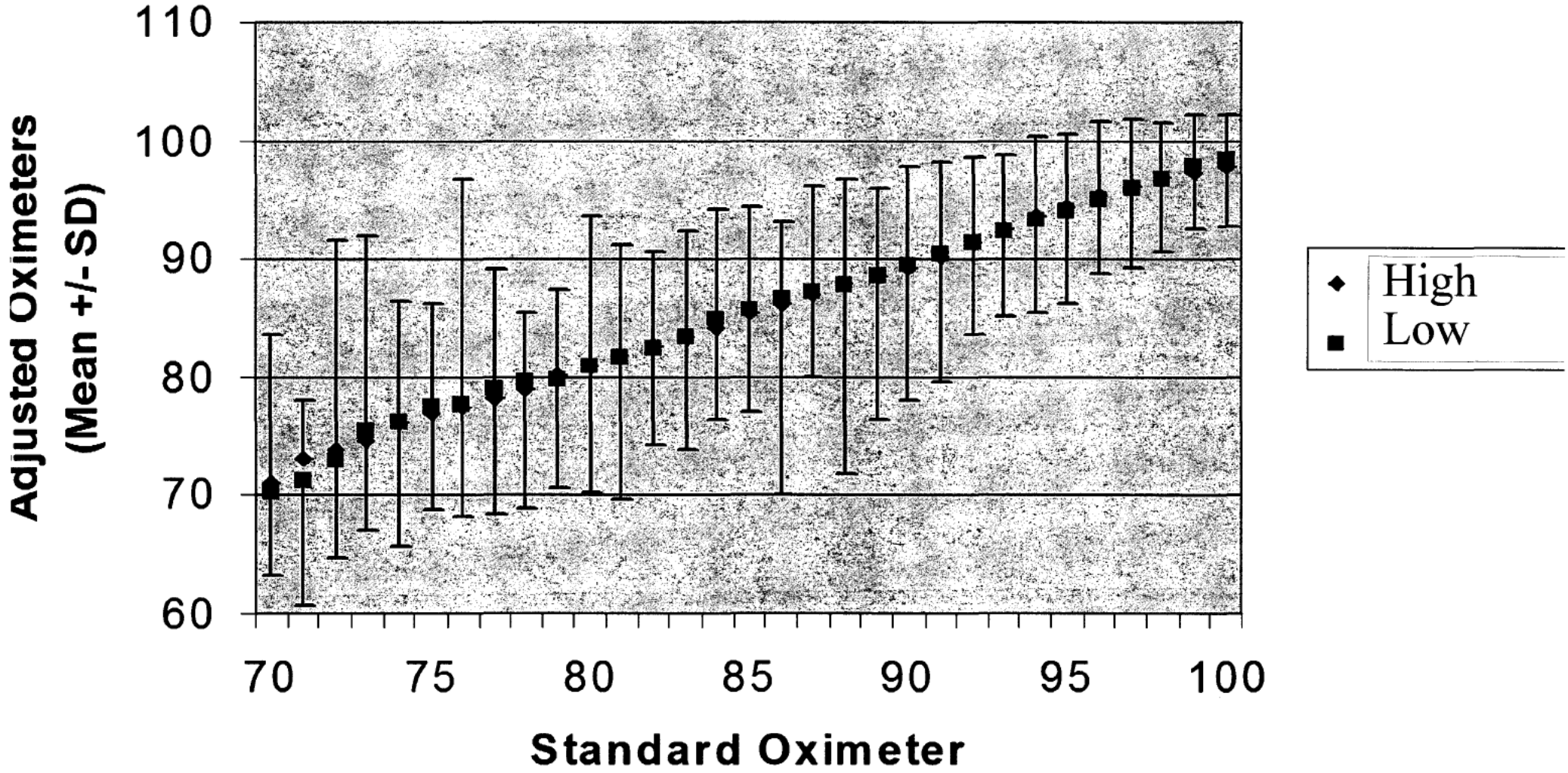
Comparison of High reading versus Low reading Oximeters Compared to a Standard Oximeter







Comparison of High reading versus Low reading Oximeters Corrected to Standard Readings



Pulse Oximetry Protocol

- **BOTH GROUPS WILL MAINTAIN DISPLAYED SATURATION AT 88-92%**
- **ALARMS FOR BOTH GROUPS WILL BE:**

  LOW – 85% HIGH - 95%

  (***Note Masimo alarms at actual limit set point, not one below*****)**
- **SPO2 READINGS BELOW 85% AND ABOVE 95% WILL BE ACTUAL, NOT ALTERED**

OXYGENATION PROTOCOL-CONT'D

- **STUDY PO WILL REMAIN WITH INFANT UNTIL OFF OXYGEN (for 3 days) or INFANT 36 WEEKS PCA whichever is sooner**
- **SpO2 FROM STUDY PO WILL BE DOWNLOADED TO RTI ONCE PER MONTH - every 2 WEEKS DURING STUDY**
- **This will contain 1 data point for SpO2 and heart rate for every 10 seconds of this 1 month interval**

Sample Size Estimate

- **The sample size depends on the outcome rate only through the standard deviation of the rate and this turns out to be essentially 50% for all subgroups (i.e. ranges from 49.7% to 50.0%). Hence one sample size table suffices for all.**
- **We will randomize by family, all multiples to same arm – we have made a 12% adjustment to sample size to account for this clustering.**

Sample Size

- **Postulating a 10% difference in primary outcome a sample size of 1310 infants will provide for 80% power for the primary as well as NDI/Mortality (Secondary Outcome)**
- **This includes a 17% attrition factor**

SUPPORT – Current Status

- ✓ Enrollment now almost 100 infants
- ✓ We have downloaded about oximeters with 2-4 weeks of data
- ✓ We are within the large target zone of 85% to 95% approximately 55% to 60% of the time
- ✓ This is the zone with the altered SpO2 values

SUPPORT – Current Status

- Downloads better done every 14 days.
- After 28 days you start to loose data!!
- Few issues with respiratory support protocols
- Oximeters – some increased alarms
- This depends on type and settings of oximeters that were previously used.

Safety Monitoring

- **We are going to monitor the occurrence of death, Grade 3 and 4 IVH, pneumothoraces in the first 14 days, the need for compressions or epinephrine in the DR.**
  DSMC has been given the rates of occurrence of each of these, overall and per strata.
- **If these occurrences are greater in any arm(s) of the trial, this information will be available to the DSMC (which has been expanded for this trial), and that arm(s) may be stopped.**

Conclusions

- **All of these studies will provide evidence to allow a determination of best practice for the ELBW Infant**
- **The best practice may differ for the infants < 26 weeks compared to infants > 26 weeks**
- **We should hold any judgments till we evaluate longer –term outcomes to avoid the mistakes of the past!!**

When Does My Alarm Sound?

Masimo

- A low alarm set at 85 alarms at 85.
- An alarm delay of up to 10 seconds may be used.
- Default low limit 90% for Neonates
- Averaging time from 2-16 seconds

Nellcor

- A low alarm set at 85 alarms at 84.
- Sat Seconds (Area under Time/Sat curve) of up to 100 seconds.
- Default low limit 80% for Neonates
- Averaging 2-4 seconds in Fast Mode, 4-7 seconds in Normal

Nellcor OxiMax

- ✓ **The *OxiMax* algorithm automatically extends the amount of data required for measuring SpO2 and pulse rate depending on the measurement conditions. During normal measurement conditions the averaging time is 6-7 seconds.**
- ✓ **During challenging measurement, conditions which could be caused by low perfusion, motion, external interference like ambient light, or a combination of these, the OXIMAX algorithm automatically extends the amount of data required beyond 7 seconds.**

Nellcor OxiMax

- ✓ If the resulting dynamic averaging time exceeds 20 seconds, the pulse search indicator is lit solid and SpO2 and Pulse Rate will continue to be updated every second.
- ✓ As these conditions become even more challenging, the amount of data required continues to extend. If the dynamic averaging time reaches 40 seconds, the pulse search indicator begins flashing, the SpO2 and pulse rate displays flash zeros indicating a loss-of-pulse condition.

Nellcor Sat Seconds

- **The SatSeconds limit controls the time that the %SpO2 level may fall outside the alarm before an audible alarm sounds.**

The method of calculation is as follows:

- **The number of percentage points that the %SpO2 falls outside of the alarm limit is multiplied by the number of seconds that the %SpO2 level remains outside that limit. This can be stated as an equation:**
- **Points x Seconds = SatSeconds**

- **Factory default low alarm limit is 80%**
- **If have a desaturation below 80%**
- **Then the oximeter counts each second**
- **A desaturation to 75% for 5 seconds**
  - 5 X 5% = 25 satseconds

Caveat Emptor

- **The *SatSeconds* "Safety Net" is for patients with saturation levels having frequent excursions below the limit, but not staying below the limit long enough for the *SatSeconds* time setting to be reached.**
- **When 3 or more limit violations occur within 60 seconds, an alarm will sound even if the *SatSeconds* time setting has not been reached.**

Masimo Oximeter

- **Has second level alarm 5% below the low alarm setting and if the SpO2 reaches this value there is an alarm with no delay – ie low alarm at 85%, then this second level alarm will sound if the SpO2 reaches 79%**

Using SatShare

- Can take signal out of Masimo oximeter for study and use Satshare cable to feed this into your normal bedside multi-parameter monitor ie Phillips, HP, etc
- The actual signal goes in as if it were the infants actual SpO2
- Thus if the Masimo is averaging at 16 seconds, each data point going in to the bedside represents the average of the previous 16 seconds with some weighting to the most current values

- **If the bedside monitor is now set to average it will further average using its own algorithm. The alarm settings will be those of the bedside monitor**
- **This is a method to avoid excessive alarms**

- **A NICU going from a Nellcor oximeter with its normal 4-7 second mode will now find that the Masimo is less responsive as it will average over a longer interval.**
- **The alarm settings will be different and there is no SatShare**
- **Thus, there may be more alarms, as the Nellcor is looking for time with an SpO2 < 80% and the Masimo will alarm with its delay at whatever it is set to, or immediately if 5% below this.**

- **Pulse Oximeters are accurate to ± 3%**
- **This it is possible to see 6% variation on new oximeters even of the same manufacture**
- **If Neonatal units in the current trial choose to set the low alarms at different levels ie < 80% as compared to 85% - the overall effect on the study will depend upon the amount of time that the infant is between 85% and 95%, and between 88% and 92%**

- **The maximum difference with the current Masimo study Oximeters will occur between about 87% and 93% and then the values slur towards normal**
- **They are normal at 84% and 96% to our testing**
- **If you maintain all infants between 80% and 85%**

There will be no difference in their SpO2 values, as these are identical values with both altered oximeters

Oximeter Information

- **The SUPPORT study group decided to set the limits of the altered oximeter values at 84% and 96% as this reflected the current practices in the various units and there was no evidence that lowering such limits was safe.**

Oximeter Information
SUPPORT Trial July 2005

- **At the present time based on the available downloads representing over 7000 hours of data we are in the range of 85% to 95% approximately 60% of the time for infants requiring oxygen, and 47% of the time for all infants irrespective of FiO2**

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@UCSD.Edu
Cc: fmartinez@UCSD.Edu
Subject: Re:
Date: Friday, August 05, 2005 7:27:10 AM

Hi Rose: that would be helpful. I have a full talk on the subject but includes very few slides specific to SUPPORT.
Wally
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
To: nfiner@UCSD.Edu <nfiner@UCSD.Edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>
CC: fmartinez@UCSD.Edu <fmartinez@UCSD.Edu>
Sent: Fri Aug 05 06:21:38 2005
Subject: RE:

Neil
I likely have the bulk of the slides you need as I have the various SUPPORT Powerpoint slides that have been developed over the last year. Let me know if you want me to go through them to develop a back-up presentation in the event you continue to have email issues.

Don't worry about the meeting. My best to you and your family.
Take care
Rose
-----Original Message-----
From: nfiner@UCSD.Edu [mailto:nfiner@UCSD.Edu]
Sent: Friday, August 05, 2005 7:02 AM
To: wcarlo@peds.uab.edu
Cc: Higgins, Rosemary (NIH/NICHD); fmartinez@UCSD.Edu
Subject:

Hi Wally
I am going to try to send you the presentation that I have been working on. Its way too long, and at present I haven't found a connection that will allow
me to load an attachment as I am in Toronton and have no good internet connection. I am still planning to be at the meeting and do this (b) (6) (b) (6) and I am uncertain as to what will happen.
Thanks for coming to this meeting. I may have to leave after my presentation

so that you could participate in any subsequent discussion.
Neil

From:	Wally Carlo, M.D.
To:	Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; Higgins, Rosemary (NIH/NICHD) [E]; Ken Poole; Michele; Neil Finer; Shahnaz Duara; Wade Rich; Wally Carlo, M.D.; nfiner@ucsd.edu
Subject:	SUPPORT Oximeter
Date:	Thursday, August 04, 2005 5:16:16 PM
Attachments:	O2 Sat data Rev 8-2-05.ppt Legends for SaO2 slides.doc

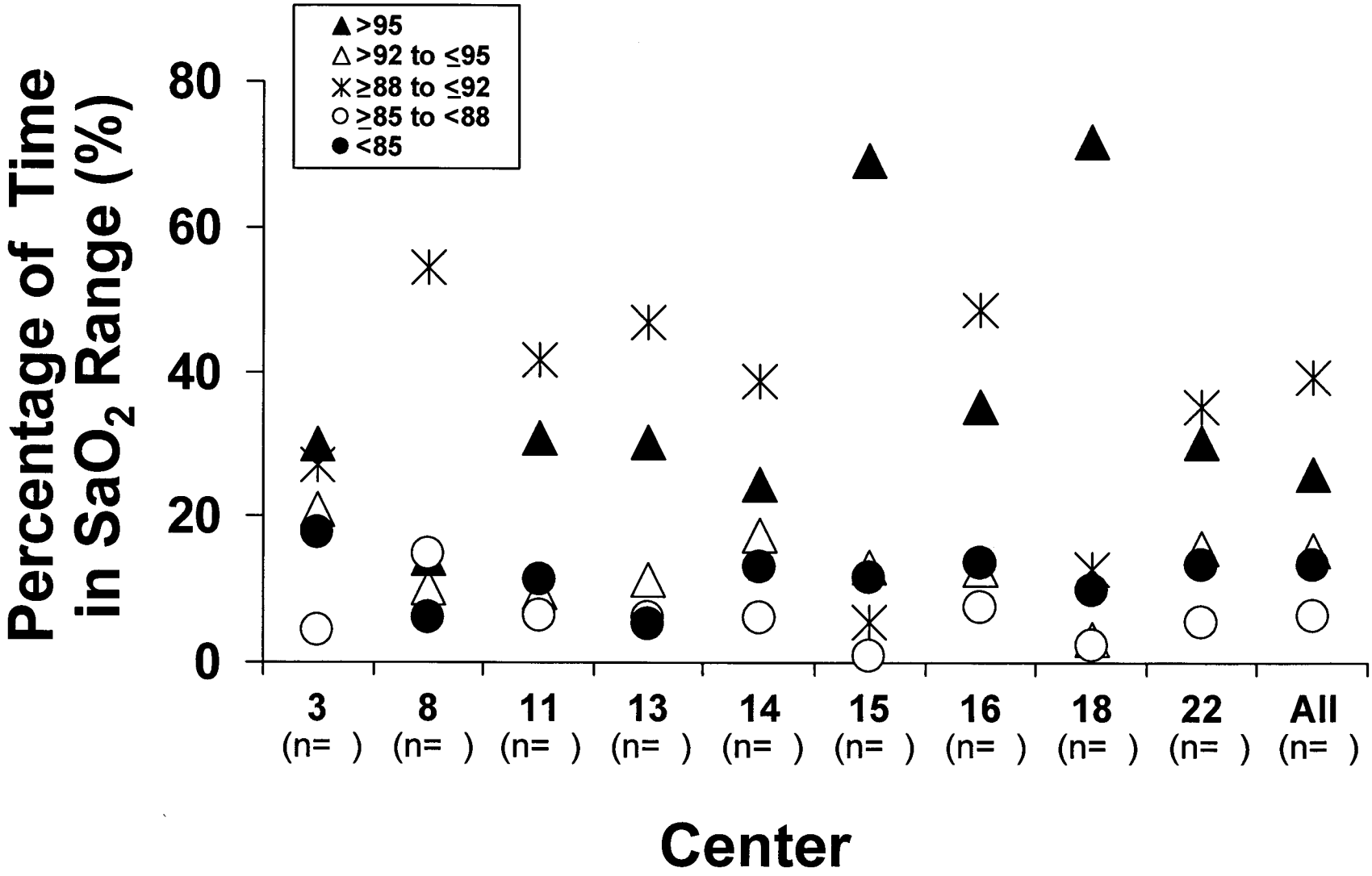
Dear All:
Thanks for your feedback. I have made minor changes on the graphs as described below and included a description to make it easier to follow and for the request to the DSMC as requested by Ken.

The changes include:

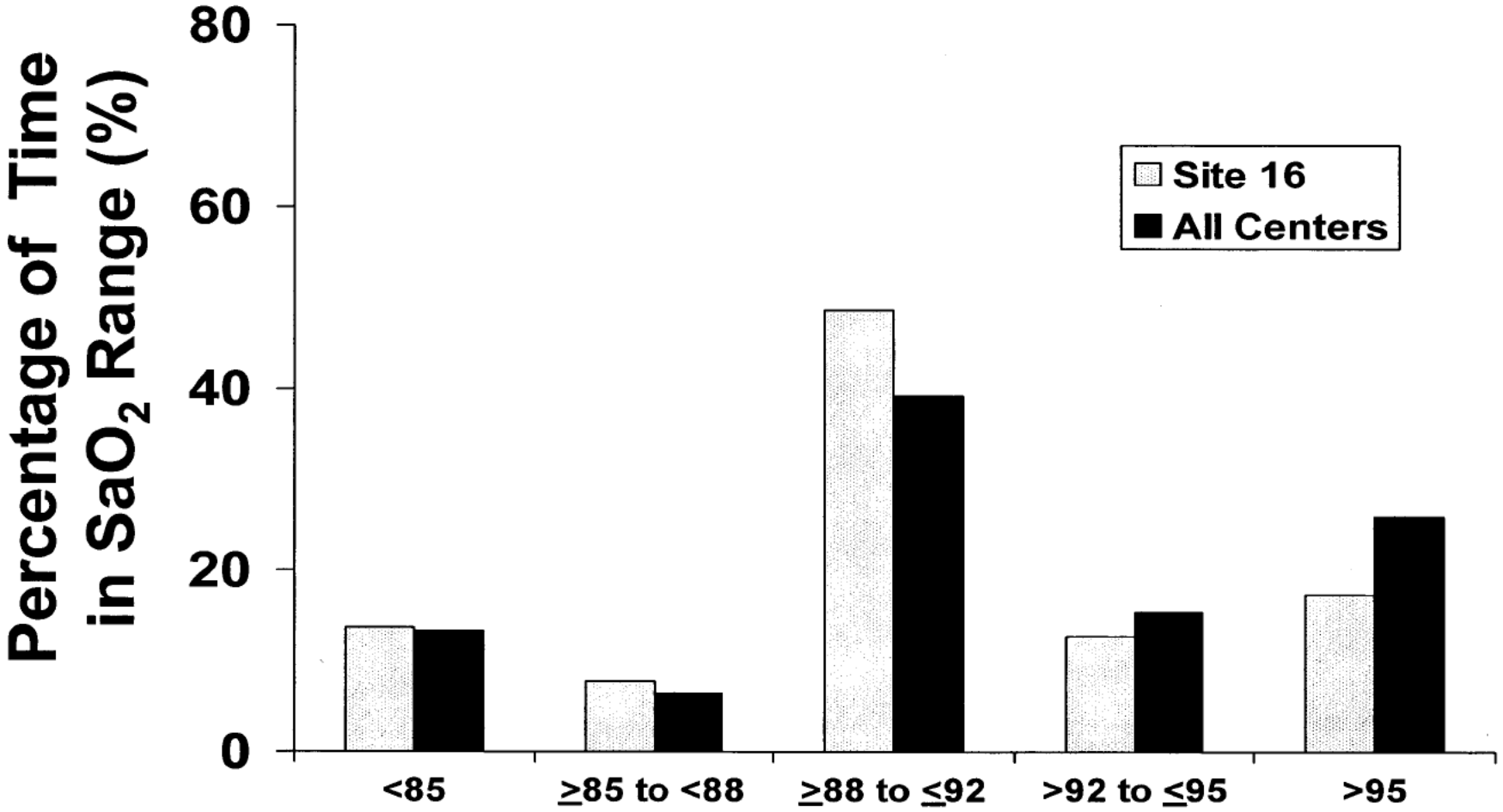
1. A title has been added to each graph to succinctly state what is depicted.
2. A detailed description (legend) of what each graph would show has been added
3. Minor changes to the x axis were made
4. The order of the graphs have been changed to make it more logical (one could argue the logic).

Thanks,
Wally

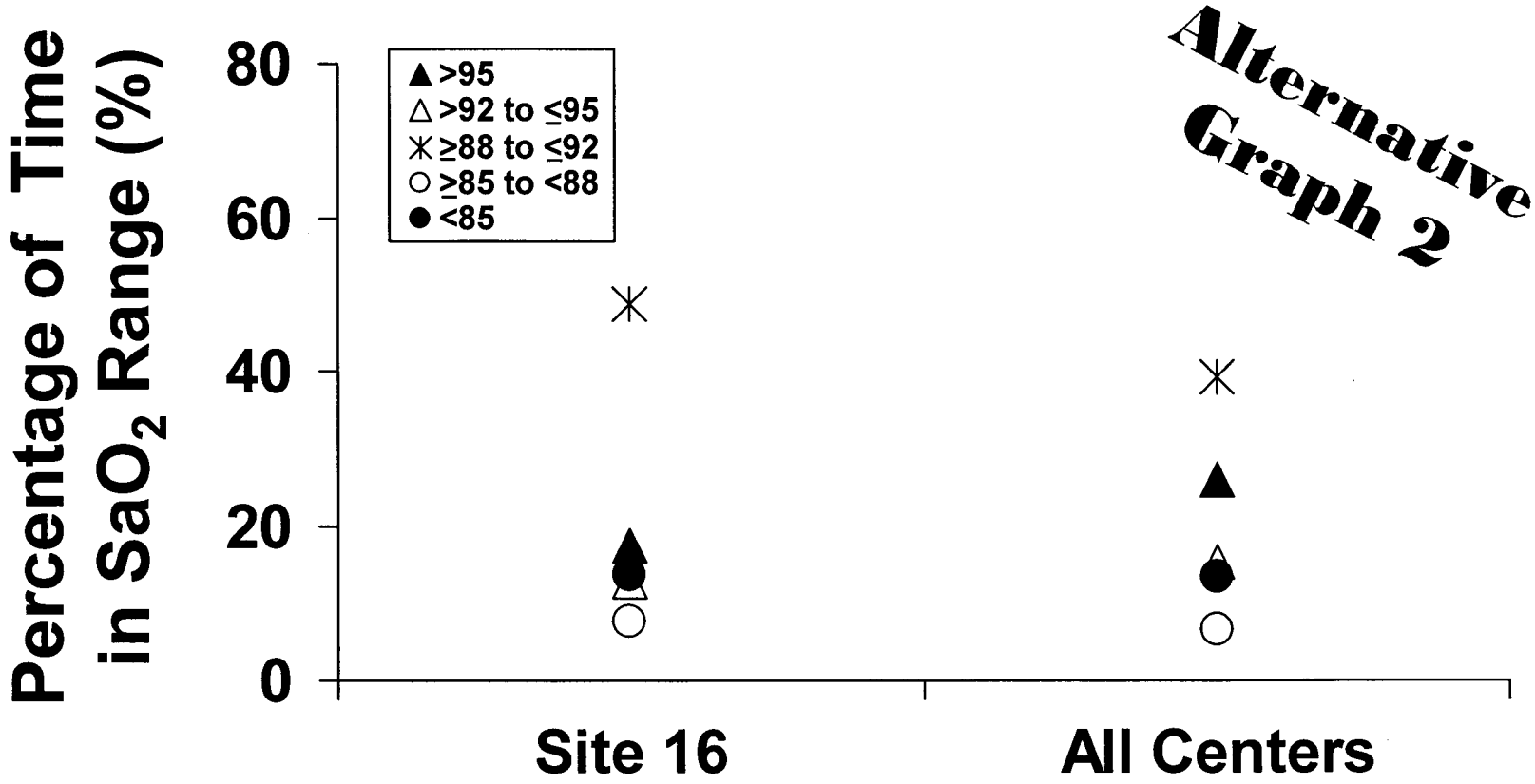
Cumulative Data of Percentage of Time in SaO_2 Ranges for each Center



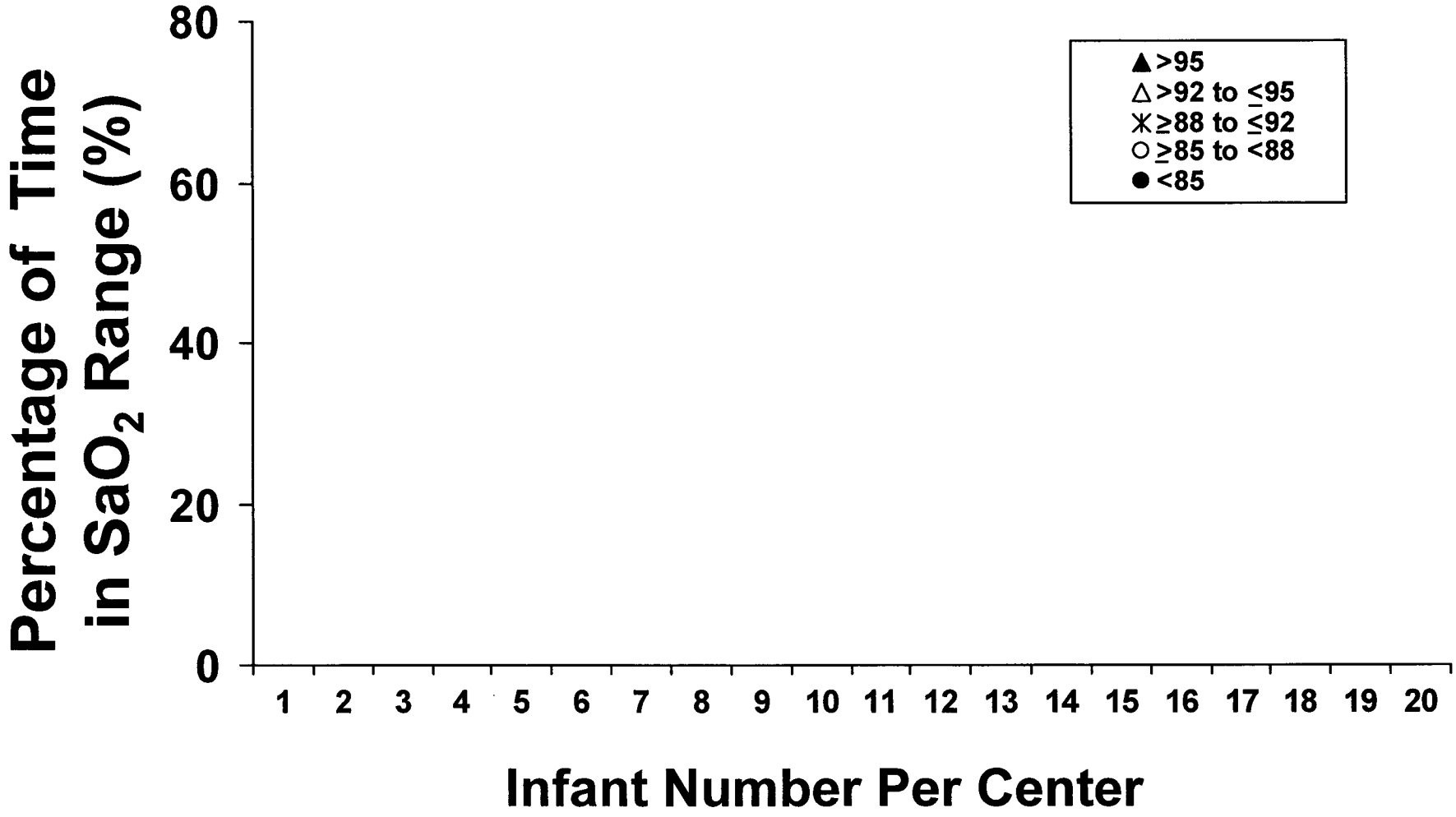
Cumulative Data of Percentage of Time in SaO_2 Ranges for Selected Centers Compared to All Center Data



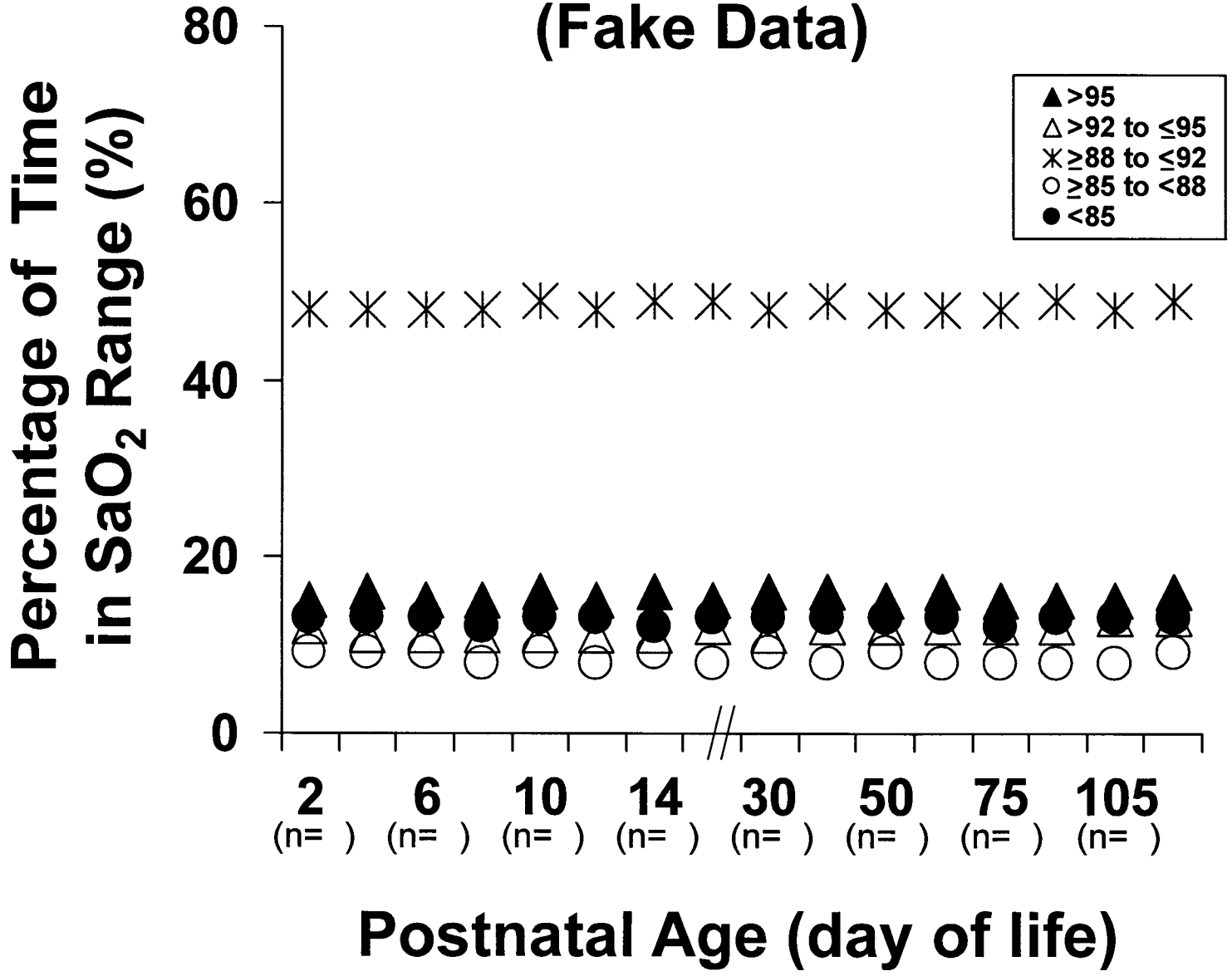
Cumulative Data of Percentage of Time in SaO_2 Ranges for Selected Centers Compared to All Center Data



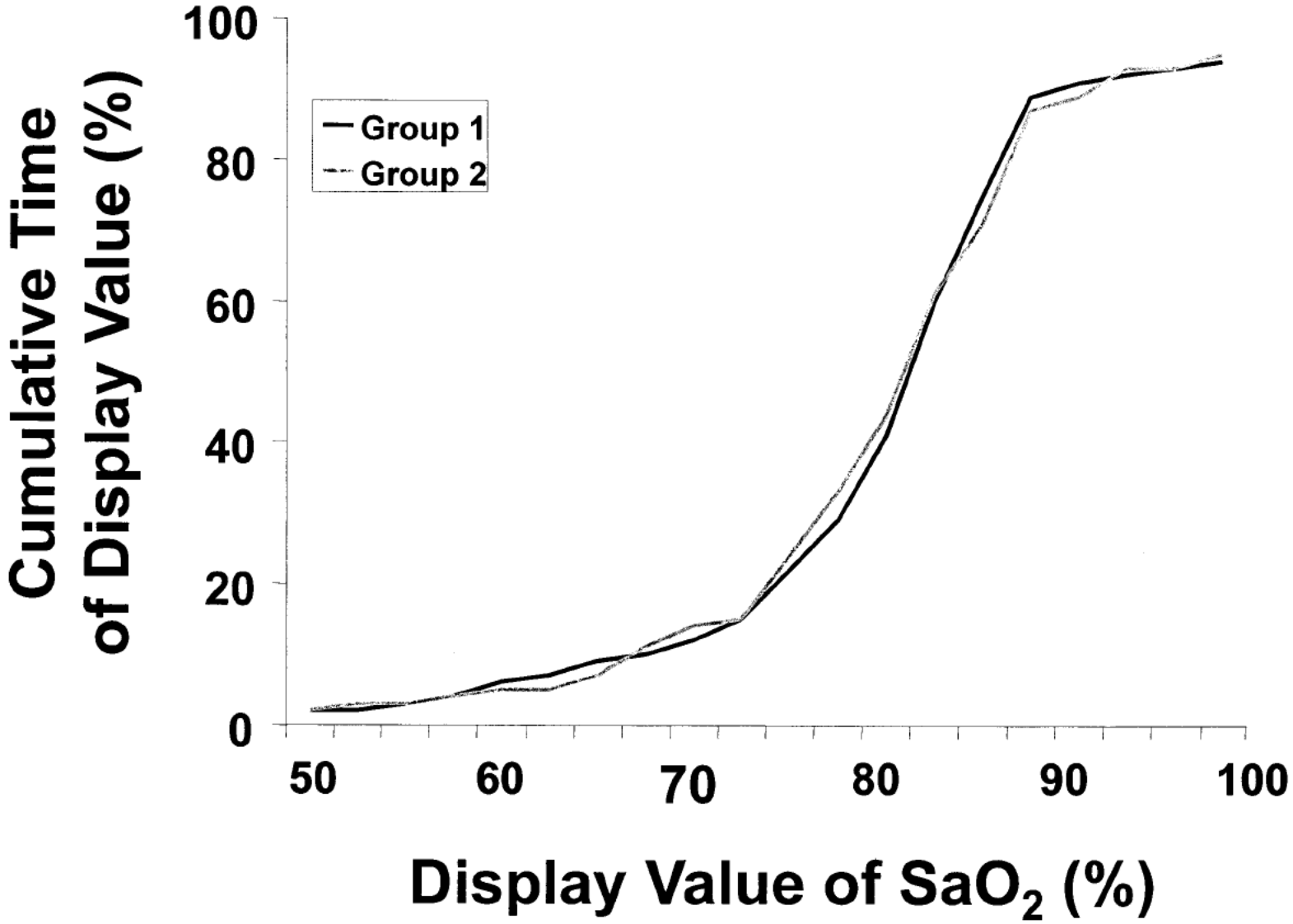
Cumulative Data by Percentage of Time in SaO_2 Ranges Depicted for Each Infant Consecutively Enrolled in Center X



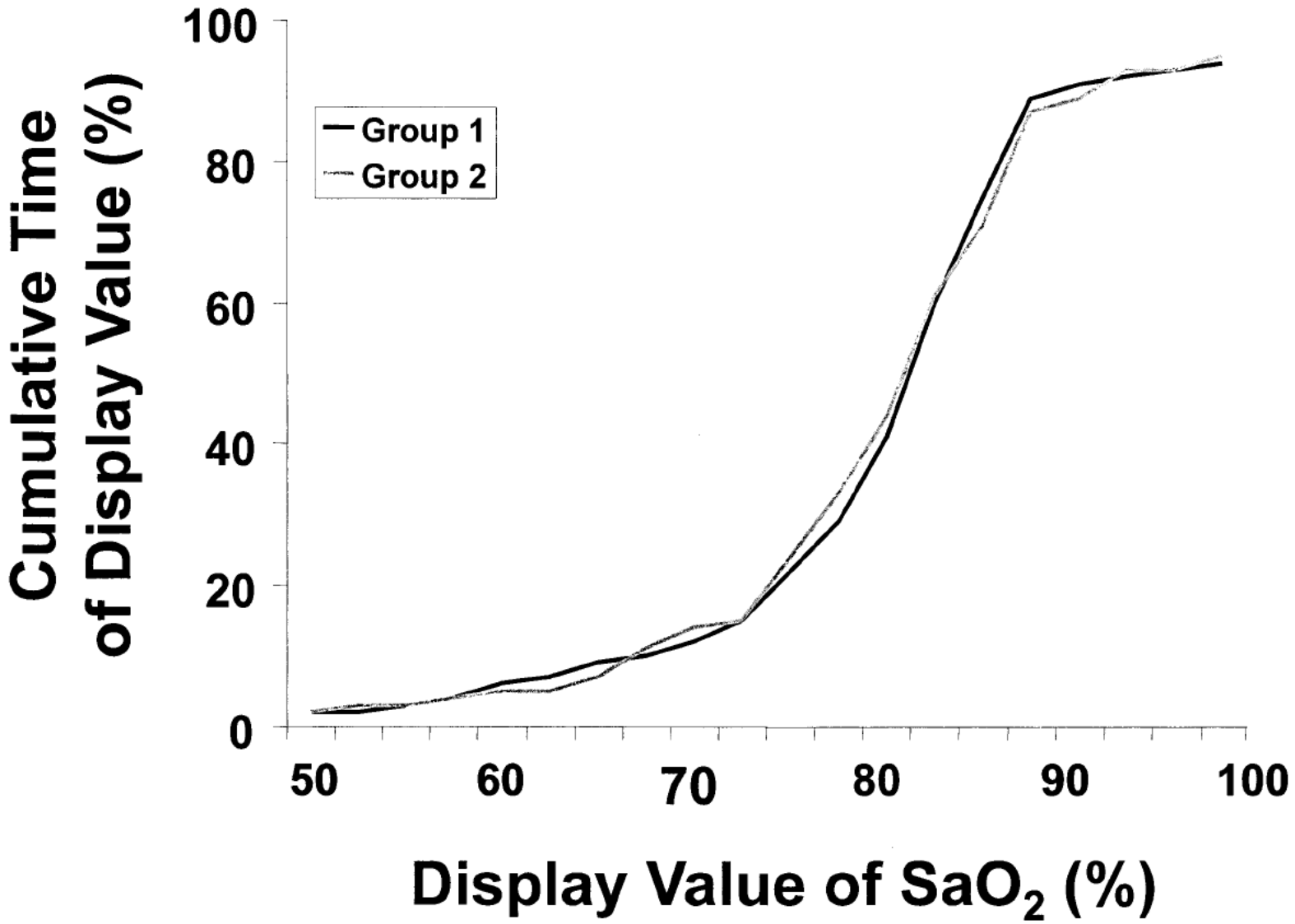
Cumulative Data of Percentage of Time in SaO_2 Ranges by Postnatal Age for All Infants in Center X (Fake Data)



Cumulative Data of Percentage of Time in Display SaO_2 Values for Infants in both Graphs for All Centers (Fake Data)



Cumulative Data of Percentage of Time in Display SaO_2 Values for Infants in both Graphs for Center X (Fake Data)



Legend

Graph 1: Cumulative data of percentage of time in SaO_2 ranges depicted for each center. The x-axis includes NRN Center number of each Center participating in SUPPORT. The number of infants (n) included per center is added under the center number. The star symbol is used for the target range. The open symbols add the ranges ($\geq$88 to $\leq$92% SaO_2) which optimized actual SaO_2 separation above (>92 to $\leq$95% SaO_2) and the range below ($\geq$85 to < 88% SaO_2) which complete the target. The closed symbols depict the range above (triangles) or below (circles) the target range (when alarms go off).

Graph 2: Cumulative of percentage of time in SaO_2 ranges depicted for selected center compared to All Center data. The symbols and ranges used are the same as in Graph 1. (We could use the same symbols and format as in Graph 1, shown as Alternative Graph 2).

Graph 3: Cumulative data of percentage of time in SaO_2 ranges depicted for each infant consecutively enrolled to date in a Center. The x-axis is the number of the consecutively enrolled infants within each center. The symbols and ranges are the same used in Graph 1.

Graph 4: Cumulative data of percentage of time in SaO_2 ranges depicted by postnatal age for all infants enrolled to date in each center. The x-axis is the postnatal age as day of life. The symbols and ranges are the same used in Graph 1. (Note that because of deaths, the number of infants decreases with postnatal age. The x-axis can be expanded as needed to included, for example each day).

Graph 5: Cumulative data of display values of SaO_2 for both groups (high and low SaO_2 display values) for All Centers. Overlapping of display values between 85 and 95 indicate good separation of total SaO_2 values.

Graph 6: Cumulative data of display values of SaO_2 for both groups (high and low SaO_2 display values) for Center X. Overlapping of display values between 85 and 95 indicate good separation of SaO_2 values.

From: Michael O`Shea
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: azithromycin BPD project
Date: Thursday, August 04, 2005 4:18:24 PM

Rose,
I think that the most efficient use of resources would be to wait for the network re-configuration and then move forward. Hopefully we would at that point be able to join the Phase 3. So I am voting for #3.
Mike

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, July 27, 2005 12:24 PM
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O`Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: Petrie, Carolyn
Subject: azithromycin BPD project

Hi,
At the last Steering committee meeting, Dr. Pablo Sanchez from UT Southwestern, Dallas presented a project on azithromycin and BPD. I need input from each of you with respect to how this should proceed. Please send me your choice of the following options by August 9, 2005:

1. Move forward with the pilots if funded
2. Move forward with pilots and main trial if funded (this impacts on SUPPORT, Inositol, and potentially probiotics which is currently under review)
3. Do not move on project at this point in time, wait for the network re-configuration (April 1, 2006)
4. Do not move forward on the project

I have reattached the proposal for your convenience.

Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Petrie, Carolyn
To: Stevens, Timothy; Hastings, Betty J.; Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: [Fwd: Re: support]
Date: Thursday, August 04, 2005 11:57:41 AM

Tim et al.

Below are some comments for the Pulmonary Outcomes study.

These are good questions. I think clarifying whether #2 includes well-child visits is important. I agree that multiple choice responses are better-might want to define occasionally and often with a range of times or just use a range of times. I would add aldactone to the med lists for both interviews. Defining whether Synagis was received in the first and/or second years of life would probably make the response clearer.
Richard

> I reviewed the SUPPORT forms and these are our comments/questions
>
>2. does this include well child vs
>
>7 and 8 we suspect that parent recall might be fuzzy and wonder if using
>multiple choice ie never, occ, often etc would give more meaningful results
>
>Meds-our children are typically on Aldactone w Diuril-do they want to add
>it to the list
>
>In addition-on 18m
>
>20 do they want to differentiate Synagis received first year vs second year
>
>25 again we question parent recall and wonder if it should be multiple
choice
>

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: [Fwd: Re: support]
Date: Thursday, August 04, 2005 11:54:25 AM

Rose-

Need some help clarifying these comments.

-----Original Message-----
From: Elaine Romano [mailto:Elaine.Romano@Yale.Edu]
Sent: Thursday, August 04, 2005 11:46 AM
To: Petrie, Carolyn
Cc: Richard A. Ehrenkranz; Joanne
Subject: [Fwd: Re: support]

Carolyn
enclosed are some comments regarding the Support forms from Rich,Joanne and myself
thanks
elaine

-------- Original Message --------
Subject: Re: support
Date: Thu, 04 Aug 2005 11:14:21 -0400
From: Richard Ehrenkranz <richard.ehrenkranz@yale.edu>
To: Elaine Romano <Elaine.Romano@Yale.Edu>
CC: Joanne <joanne.williams@yale.edu>
References:<42F229E3.4060205@Yale.Edu>

These are good questions. I think clarifying whether #2 includes well-child visits is important. I agree that multiple choice responses are better-might want to define occasionally and often with a range of times or just use a range of times. I would add aldactone to the med lists for both interviews. Defining whether Synagis was received in the first and/or second years of life would probably make the response clearer.
Richard

At 10:44 AM 8/4/2005, Elaine Romano wrote:
>Dear Boss,
>Joanne and I reviewed the SUPPORT forms and these are our comments/questions
>
>2. does this include well child vs
>
>7 and 8 we suspect that parent recall might be fuzzy and wonder if using >multiple choice ie never, occ, often etc would give more meaningful results
>
>Meds-our children are typically on Aldactone w Diuril-do they want to add >it to the list
>
>In addition-on 18m
>
>20 do they want to differentiate Synagis received first year vs second year
>
>25 again we question parent recall and wonder if it should be multiple choice
>
>thanks
>e
>
>
>

>
>The information contained in this message may be privileged and
>confidential. If you are NOT the intended recipient, please notify the
>sender immediately with a copy to hipaa.security@yale.edu and destroy this
>message. Please be aware that email communication can be intercepted in
>transmission or misdirected. Your use of email to communicate protected
>health information to us indicates that you acknowledge and accept the
>possible risks associated with such communication. Please consider
>communicating any sensitive information by telephone, fax or mail. If you
>do not wish to have your information sent by email, please contact the
>sender immediately.
>
>

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

--

From: Petrie, Carolyn
To: Petrie, Carolyn; Richard Ehrenkranz; Phelps, Dale; Neil Finer; Michael O`Shea; Shankaran, Seetha; jon.e.tyson@uth.tmc.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth
Cc: Ktownsen@med.wayne.edu; Alice.J.Reardon@uth.tmc.edu; fmartinez@ucsd.edu; Hastings, Betty J.; Zaterka-Baxter, Kristin
Subject: RE: protocol review: probiotics & growth secondary to support
Date: Thursday, August 04, 2005 9:10:01 AM

Reminder for Today's call:

The protocol review conference call to discuss the protocols:

- Probiotics
- Growth secondary to SUPPORT

Is scheduled for:

Thursday, August 4
3:00-5:00pm ET

To join the call:
Dial Tollfree: **866-675**(b) (6)
Passcode: (b) (6) (# when prompted)

Leader: Rose Higgins

From: nfiner@UCSD.Edu
To: wrich@UCSD.Edu; "Wally Carlo, M.D."; "Poole, W. Kenneth"; nfiner@UCSD.Edu; "Avroy A. Fanaroff, M.D."; edward.donovan@chmcc.org; "Duara, Shahnaz"; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximetry data
Date: Wednesday, August 03, 2005 10:09:06 PM

>I would suggest that we do not record as an SAE as we know that the occurrence will be about 8-10% as will most of the other safety issues.
Neil

SUPPORT Subcommittee,
> As we are gathering it anyway, should we consder a pneumothorax an SAE
> for purposes of this trial, or simply an adverse event?
> wade
>
> _____
>
> From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
> Sent: Wednesday, August 03, 2005 2:18 PM
> To: Poole, W. Kenneth; nfiner@ucsd.edu; wrich@ucsd.edu
> Cc: Das, Abhik; Hastings, Betty J.
> Subject: RE: Oximetry data
>
>
> Hi:
>
> Yes, I can work on the request. I already got feedback from Abhik and
> Shanaz. I will wait to hear from others and then do the first draft of the
> document if ok with everyone.
>
> wally
>
> _____
>
> From: Poole, W. Kenneth [mailto:poo@rti.org]
> Sent: Wednesday, August 03, 2005 2:39 PM
> To: nfiner@ucsd.edu; wrich@ucsd.edu; Wally Carlo, M.D.
> Cc: Das, Abhik; Hastings, Betty J.
> Subject: Oximetry data
>
>
>
> Dear All,
> At the DSMC call today for the Phototherapy Trial, I asked them about
> SUPPORT study PI's viewing oximetry (and other?) data by treatment to assess
> treatment separation. They didn't seem to have a problem with the oximetry
> data but hesitated on this until they receive in writing exactly what data
> are requested. Since I'm not sure what beyond the oximetry data is being
> requested, it appears that one of you (NF,WR,WC) will have to create this
> document. If one of you will do this and forward it to me, we will get it to
> the DSMC.
>
>

From: Duara, Shahnaz
To: Wally Carlo, M.D.; nfiner@ucsd.edu
Cc: Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; Higgins, Rosemary (NIH/NICHD) [E]; Ken Poole; Michele; Shahnaz Duara; Wade Rich
Subject: RE: SUPPORT Oximeter downloads
Date: Wednesday, August 03, 2005 12:55:33 PM

Hi Wally,

I think the slides look good and will clearly present the data. On slide 2, I would add n=..., by center, on the X axis, under center number. This will help to keep a rolling tab of numbers enrolled and better clarify subject composition of the 'total group' value in slide 4.

Shahnaz

> -----Original Message-----
> **From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
> **Sent:** Tuesday, August 02, 2005 5:50 PM
> **To:** nfiner@ucsd.edu; Duara, Shahnaz
> **Cc:** Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; higginsr@mail.nih.gov; Ken Poole; Michele; Shahnaz Duara; Wade Rich
> **Subject:** RE: SUPPORT Oximeter downloads
>
> Hi everyone:
> Here is the last draft of the proposed monitoring analysis. Let me know what you think.
> Wally

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, August 01, 2005 4:01 PM
To: 'Duara, Shahnaz'
Cc: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; Wally Carlo, M.D.
Subject: RE: SUPPORT Oximeter downloads

I think that Wally wants to write something about this – I will let him put together a package.
Neil

From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Monday, August 01, 2005 12:19 PM
To: Neil Finer
Subject: RE: SUPPORT Oximeter downloads

I think its fine to send the slides out at this time. How about also plotting center performance against group total, and sending out customized slides to centers already enrolling?

Shahnaz

> -----Original Message-----
> **From:** Neil Finer [mailto:nfiner@ucsd.edu]
> **Sent:** Saturday, July 23, 2005 7:28 PM
> **To:** 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
> **Subject:** SUPPORT Oximeter downloads
>
> Hi Everyone
> I would like to send out this 2 slide presentation with Maria's data to all centers

What do you think? Is it too early? I would like to have the sites aware that we are looking at the data, as it may help them educate their staffs.
Your thoughts
Thanks
Neil

From: Wally Carlo, M.D.
To: Wally Carlo, M.D.; nfiner@ucsd.edu; Duara, Shahnaz
Cc: Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; Higgins, Rosemary (NIH/NICHD) [E]; Ken Poole; Michele; Shahnaz Duara; Wade Rich
Subject: RE: SUPPORT Oximeter downloads
Date: Wednesday, August 03, 2005 8:59:16 AM

I forgot to mention that data on slide 5 is made up. wally

From: Wally Carlo, M.D.
Sent: Tuesday, August 02, 2005 4:50 PM
To: 'nfiner@ucsd.edu'; 'Duara, Shahnaz'
Cc: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Shahnaz Duara'; 'Wade Rich'
Subject: RE: SUPPORT Oximeter downloads

Hi everyone:
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Wally

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, August 01, 2005 4:01 PM
To: 'Duara, Shahnaz'
Cc: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; Wally Carlo, M.D.
Subject: RE: SUPPORT Oximeter downloads

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Neil

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Sent: Monday, August 01, 2005 12:19 PM
To: Neil Finer
Subject: RE: SUPPORT Oximeter downloads

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Shahnaz

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> **From:** Neil Finer [mailto:nfiner@ucsd.edu]
> **Sent:** Saturday, July 23, 2005 7:28 PM
> **To:** 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
> **Subject:** SUPPORT Oximeter downloads
>
> Hi Everyone
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> Your thoughts
> Thanks
> Neil

From: Wally Carlo, M.D.
To: nfiner@ucsd.edu; Duara, Shahnaz
Cc: Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; Higgins, Rosemary (NIH/NICHD) [E]; Ken Poole; Michele; Shahnaz Duara; Wade Rich
Subject: RE: SUPPORT Oximeter downloads
Date: Tuesday, August 02, 2005 5:49:37 PM
Attachments: O2 Sat data Rev 8-2-05.ppt

Hi everyone:
Here is the last draft of the proposed monitoring analysis. Let me know what you think.
Wally

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, August 01, 2005 4:01 PM
To: 'Duara, Shahnaz'
Cc: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; Wally Carlo, M.D.
Subject: RE: SUPPORT Oximeter downloads

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Neil

From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Monday, August 01, 2005 12:19 PM
To: Neil Finer
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> **From:** Neil Finer [mailto:nfiner@ucsd.edu]
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> **To:** 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
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> Hi Everyone
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> What do you think? Is it too early? I would like to have the sites aware that we are looking at the data, as it may help them educate their staffs.
> Your thoughts
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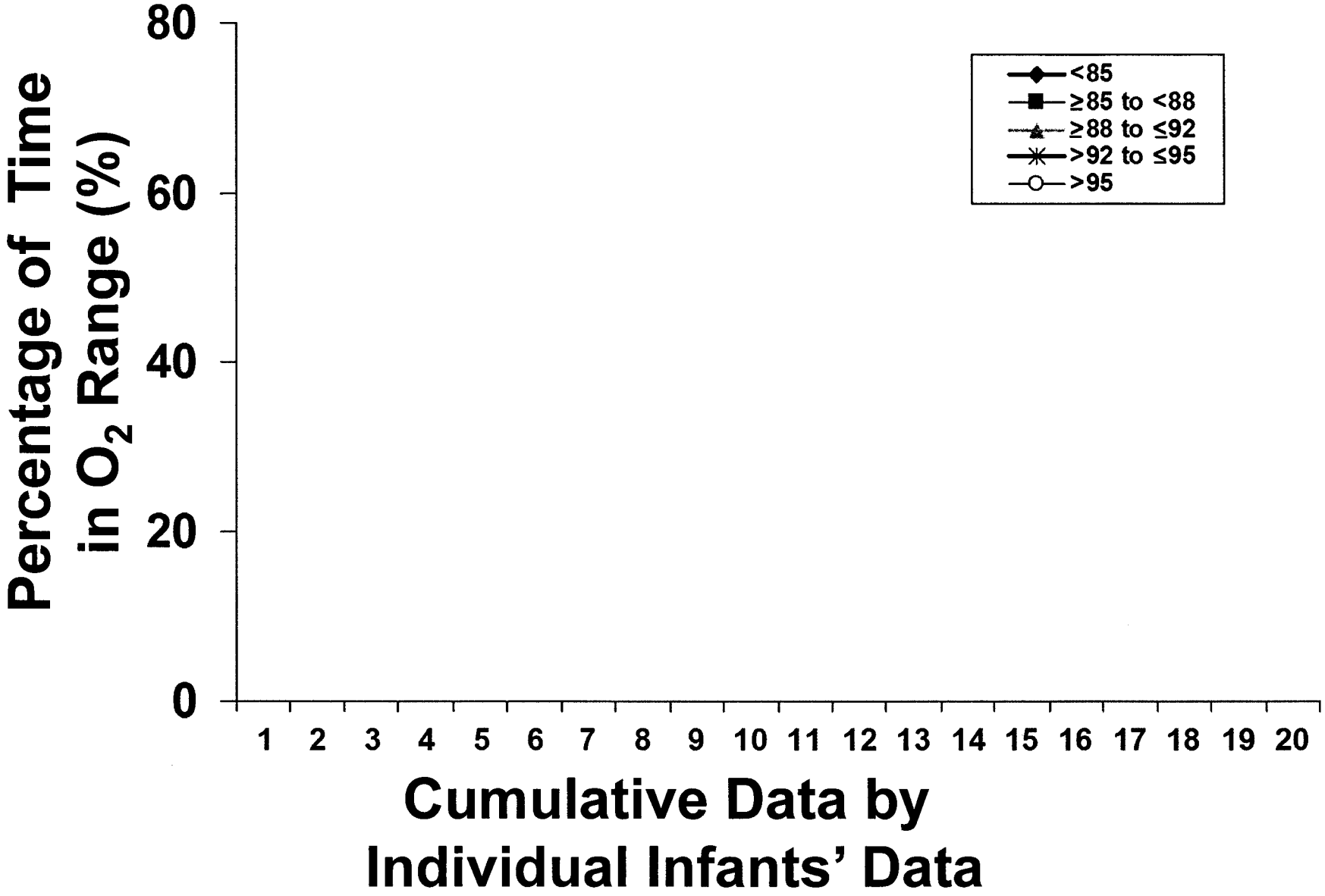
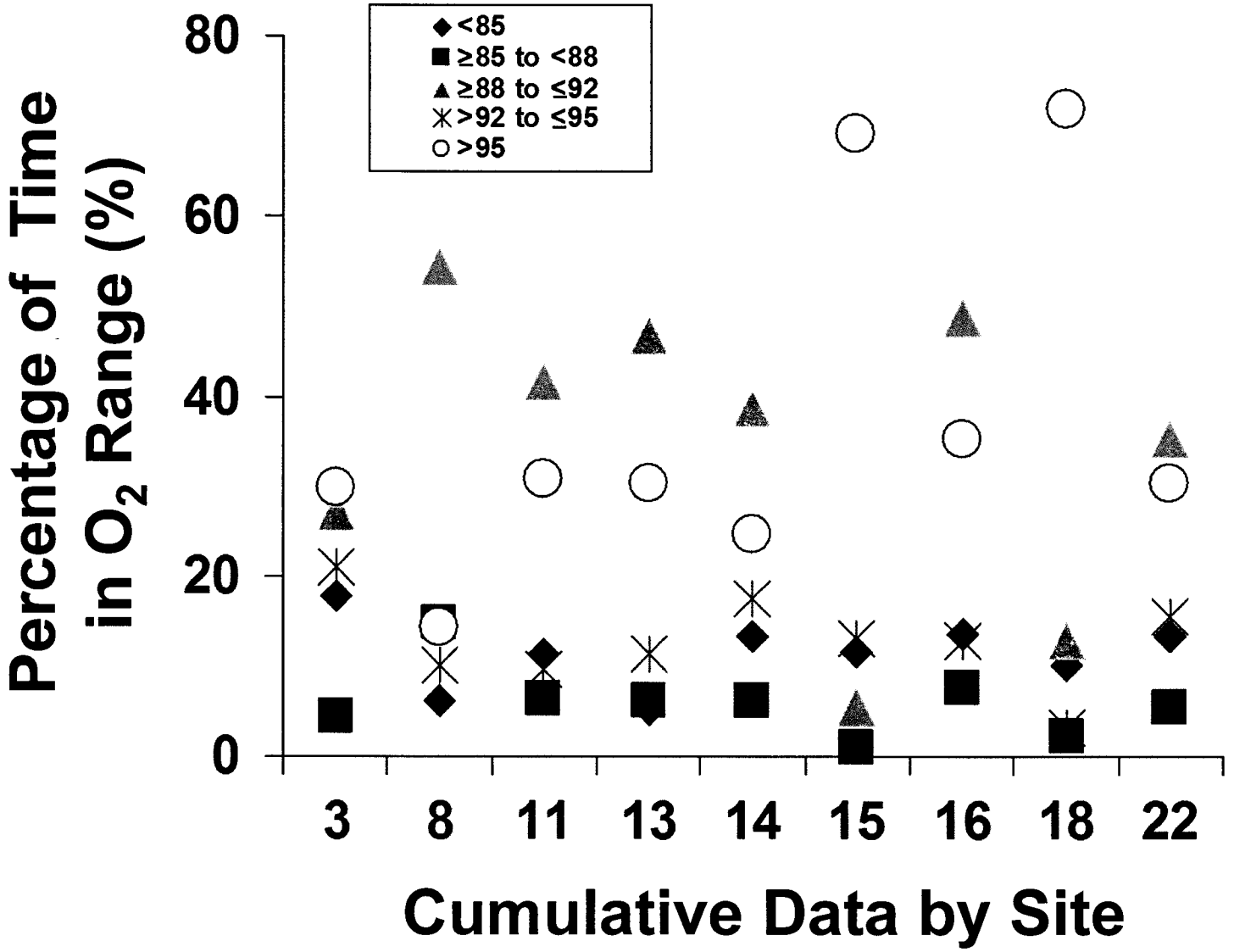
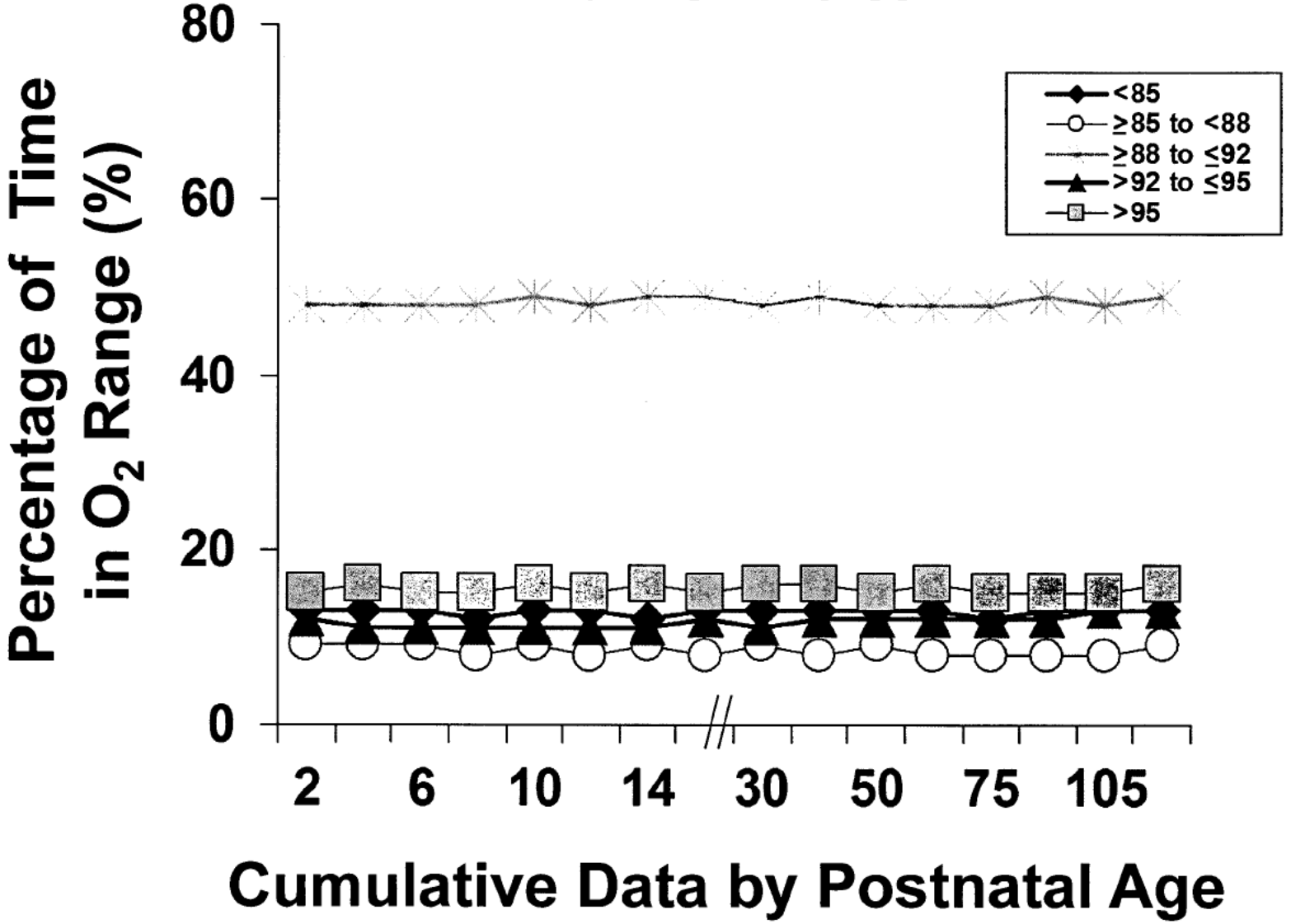
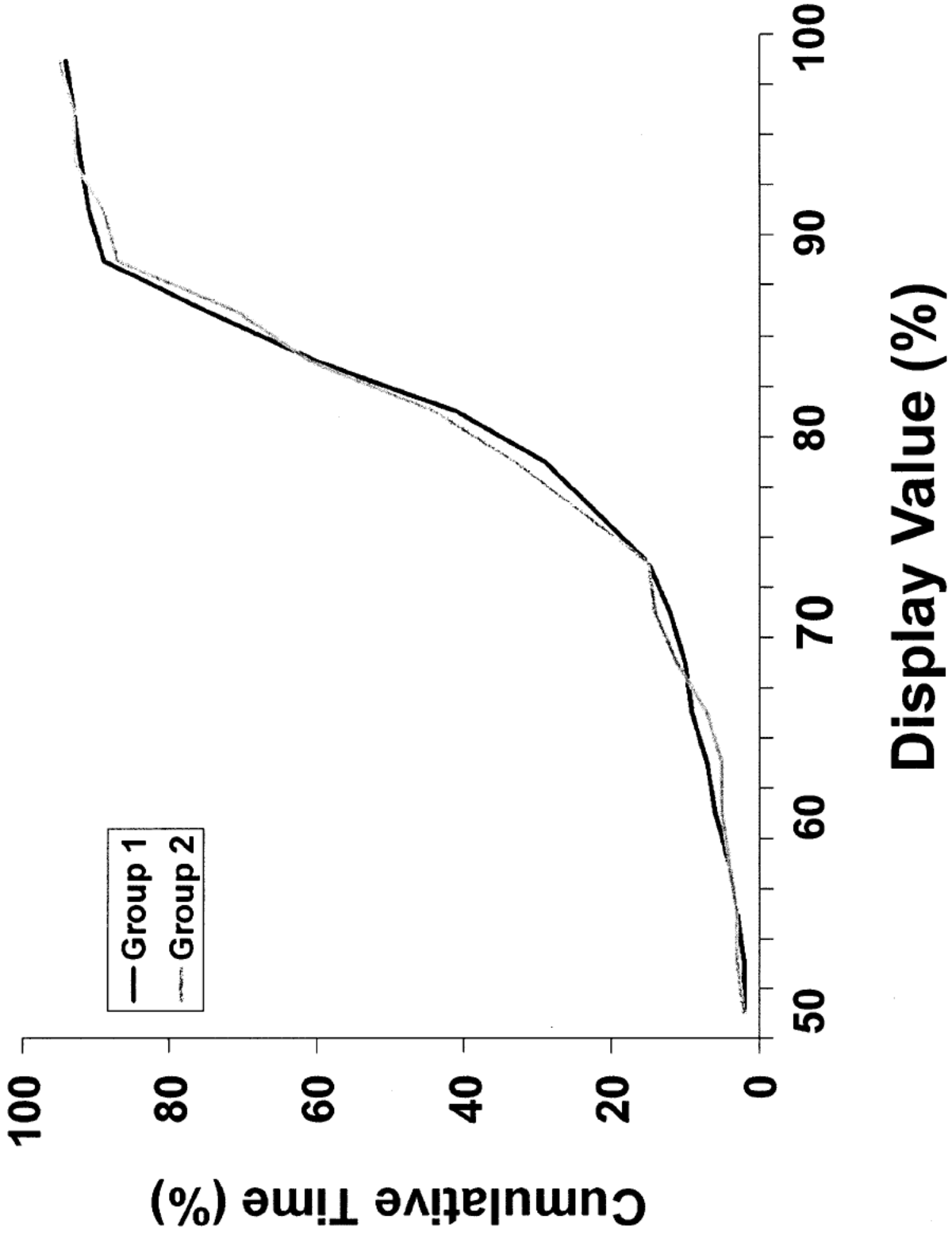
> Neil





Fake Data





From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: protocol review: probiotics & growth secondary to support
Date: Tuesday, August 02, 2005 2:07:36 PM

---

fyi

-----Original Message-----
From: Fernando Martinez [mailto:fmartinez@ucsd.edu]
Sent: Tuesday, August 02, 2005 2:06 PM
To: Petrie, Carolyn
Cc: Neil Finer; Wade Rich
Subject: RE: protocol review: probiotics & growth secondary to support

Hello Carolyn,

Dr. Finer (b) (6) and may not be able to participate in either of the calls; however, he said he would do his best to make them.

Fernando

Fellowship Coordinator
Division of Neonatology
UCSD Medical Center
402 W. Dickinson St., MPF 1-140
San Diego, CA 92103-8774
619.543.3285 Telephone
619.543.3812 Facsimile

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Thursday, June 30, 2005 2:32 PM
To: Petrie, Carolyn; Richard Ehrenkranz; Phelps, Dale; Neil Finer; Michael O`Shea; Shankaran, Seetha; jon.e.tyson@uth.tmc.edu; higginsr@mail.nih.gov; Das, Abhik; Poole, W. Kenneth
Cc: Ktownsen@med.wayne.edu; Alice.J.Reardon@uth.tmc.edu; Fernando Martinez
Subject: protocol review: probiotics & growth secondary to support

The protocol review conference call to discuss the protocols:

- Probiotics
- Growth secondary to SUPPORT

Is scheduled for:

Thursday, August 4
3:00-5:00pm ET

To join the call:
Dial Tollfree: **866-675**(b) (6)
Passcode: [redacted](# when prompted)

Leader: Rose Higgins

From: Petrie, Carolyn
To: Petrie, Carolyn; Das, Abhik; Poole, W. Kenneth; Gantz, Marie; Schaefer, Scott E.; wrich@ucsd.edu; Neil Finer
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Hastings, Betty J.; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Oximetry call Wed Jul 27, 1-2pm ET
Date: Tuesday, July 26, 2005 11:25:07 AM

Reminder:

The SUPPORT Oximetry call to discuss the function of oximeters and downloads is scheduled for

Wednesday, July 27
1:00-2:00 pm ET (10:00-11:00 am PT)

To join the call:
Dial Tollfree: **866-675-**(b) (6)
Passcode: (b) (6) (# when prompted)

Leader: Rose Higgins

From: Neil Finer
To: "Wally Carlo, M.D."
Cc: "Ken Poole"; "Shahnaz Duara"; "Donovan, Edward (DONOVAEF)"; "Avroy A. Fanaroff, M.D."; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich; "Michele Walsh"; "Betty Hastings"
Subject: RE: SUPPORT Oximeter downloads
Date: Tuesday, July 26, 2005 11:06:42 AM

Wally
Have we in the past looked at accumulating data in an RCT apart from the DSMC evaluations? This would require having the PaCO2 by group although not identified, and we would have to know which values we wanted – ie before or after intubation extubation etc.
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, July 26, 2005 4:43 AM
To: Neil Finer
Cc: Ken Poole; Shahnaz Duara; Donovan, Edward (DONOVAEF); Avroy A. Fanaroff, M.D.; Rosemary Higgins; Wade Rich; Michele Walsh; Betty Hastings
Subject: RE: SUPPORT Oximeter downloads

Neil: We may want to know if there is enough separation. Maybe more education and feedback on preventing contamination would be helpful. Wally

---

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, July 25, 2005 11:10 PM
To: Wally Carlo, M.D.
Cc: Ken Poole; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Donovan, Edward (DONOVAEF); Avroy A. Fanaroff, M.D.; Rosemary Higgins; Wade Rich; Michele Walsh; Betty Hastings
Subject: Re: SUPPORT Oximeter downloads

Hi Wally
I do not believe that we should review study data that is not for safety. The downloads were designed to be available to us as feedback, and we can look at them without breaking the randomization as we look at the readout values, not the corrected values. If we look at PaCO2 overall, we will learn very little. To be meaningful we would need to know the levels of PaCO2 by the 2 vent groups, and I think that we would not want to look at such information at present. I need guidance here as to what we can and should legitimately look at. I will ask Rose to set up a call over the next 2 weeks.
Regards
Neil

> ----- Original Message -----
> **From:** Wally Carlo, M.D.
> **To:** higginsr@mail.nih.gov ; nfiner@UCSD.EDU ; AAF2@po.cwru.edu ; bkh@rti.org ; Edward.Donovan@chmcc.org ; poo@rti.org ; mcw3@po.cwru.edu ; sduara@miami.edu ; wrich@UCSD.EDU
> **Cc:** petrie@rti.org
> **Sent:** Monday, July 25, 2005 6:17 AM
> **Subject:** Re: SUPPORT Oximeter downloads
>
> I think we should. I also think some analysis of the vent intervention (eg CO2 levels) should be done. 9
> Wally
> Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
To: Neil Finer <nfiner@ucsd.edu>; 'Avroy A. Fanaroff, M.D.' <aaf2@po.cwru.edu>; 'Betty Hastings' <bkh@rti.org>; 'Ed Donovan' <Edward.Donovan@chmcc.org>; 'Ken Poole' <poo@rti.org>; 'Michele' <mcw3@po.cwru.edu>; 'Shahnaz Duara' <sduara@miami.edu>; 'Wade Rich' <wrich@ucsd.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>
CC: Petrie, Carolyn <petrie@rti.org>
Sent: Mon Jul 25 07:35:08 2005
Subject: RE: SUPPORT Oximeter downloads

Neil and others,

Should we set up a call in the next few weeks to discuss?
Thanks

Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Saturday, July 23, 2005 7:28 PM
To: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; Higgins, Rosemary (NIH/NICHD); 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
Subject: SUPPORT Oximeter downloads

Hi Everyone

I would like to send out this 2 slide presentation with Maria's data to all centers

What do you think? Is it too early? I would like to have the sites aware that we are looking at the data, as it may help them educate their staffs.

Your thoughts

Thanks

Neil

From: Wade Rich
To: "Das, Abhik"; "Poole, W. Kenneth"; nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Oximeter downloads
Date: Tuesday, July 26, 2005 10:42:14 AM
Attachments: Oximeter downloads.xls

Abhik,

We have reviewed 33 Support oximetry downloads at our center. 4 studies were truncated. All were of a duration of 30 days or greater. I believe that my original plan, which was to download every 4 weeks instead of every 30 days would have worked, but it leaves little room for error. Unless there is a rebelion on the Coordinator's call this week, I think it would be appropriate to continue to download every 2 weeks.

Wade

Pt ID	Oximeter Start Date	Recording Start Date	Recording Start Time	Oximeter D/C'd	Download Date	Download Time
(b) (6)	(b) (6)	(b) (6)	13:50:54	(b) (6)	(b) (6)	17:41
	(b) (6)		9:52:04			10:12
	(b) (6)		22:35:36			20:25
	(b) (6)		11:03:33			13:06
	(b) (6)		12:51:49			10:22
	(b) (6)		15:33:56			12:23
	(b) (6)	(b) (6)	9:25:02			9:51
	(b) (6)		9:17:46			14:09
	(b) (6)		14:53:16			12:25
	(b) (6)		15:50:11			9:22
	(b) (6)		11:39:33			10:44
	(b) (6)		9:56:55			12:07
	(b) (6)		12:44:35			12:45
	(b) (6)		12:52:29			9:25
	(b) (6)		3:35:31			11:21
	(b) (6)		12:21:37			15:34
	(b) (6)		16:01:20			17:18
	(b) (6)	Data download error!	Data the same as (b) (6)			
	(b) (6)		23:03:11			13:59
			14:40:25			14:26
			15:26			15:56
			10:12:33			16:57
			17:20:20			11:46
			12:16:15			10:43
			11:55:43	(b) (6)		14:08
			22:14:28			14:03

(b) (6)

(b) (6)

16:31:53
9:05:09

21:24:52

6:51:35

6:18:28

5:24:05
14:30:34

(b) (6)

13:07
10:37

14:57

13:44

15:06

14:28
10:12

From:	Neil Finer
To:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Subject:	SUPPORT Oximeter downloads
Date:	Saturday, July 23, 2005 7:28:46 PM
Attachments:	July Downloads.ppt Time in range for supp O2 7-13-05.rtf Time in range for all 7-13-05.rtf

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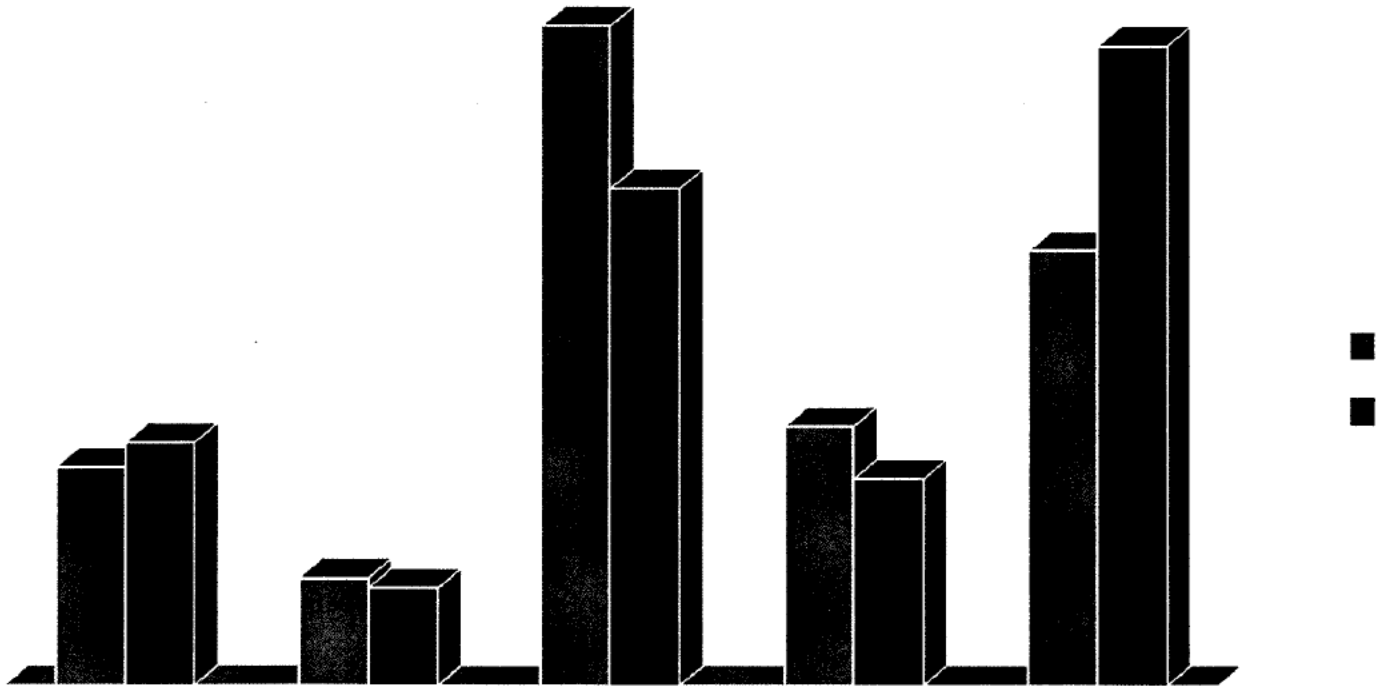
Hi Everyone
I would like to send out this 2 slide presentation with Maria's data to all centers
What do you think? Is it too early? I would like to have the sites aware that we are looking at the data, as it may help them educate their staffs.
Your thoughts
Thanks
Neil

Oximeter Information
SUPPORT Trial July 2005

- **At the present time based on the available downloads representing over 7000 hours of data we are in the range of 85% to 95% approximately 60% of the time for infants requiring oxygen, and 47% of the time for all infants for whom there is data .**

Percent of Time at Target SpO2s
SUPPORT Trial



PERCENT OF TIME SPENT IN EACH RANGE (OXIMETER DISPLAY)
DAYS ON SUPPLEMENTAL 02 (STUDY DAYS 1-14 ONLY)

Center Number	Total number of hours	TARGET				
		<85	>=85 and <88	>=88 and <=92	>92 and <=95	>95
3	834.9	17.8	4.5	27.0	20.9	29.9
8	171.3	6.2	14.8	54.5	10.1	14.3
11	752.6	11.4	6.5	41.7	9.6	30.8
13	166.9	5.2	6.2	46.8	11.4	30.4
14	2123.6	13.2	6.2	38.6	17.4	24.5
15	1.8	11.6	0.9	5.4	13.0	69.1
16	1396.9	13.6	7.7	48.7	12.7	17.3
18	32.1	10.0	2.2	12.8	3.2	71.9
22	1668.2	13.4	5.5	35.1	15.6	30.4
Total	**7148.3**	**13.3**	**6.4**	**39.2**	**15.3**	**25.9**

PERCENT OF TIME SPENT IN EACH RANGE (OXIMETER DISPLAY)
ALL DATA

Center Number	Total number of hours	<85	>=85 and <88	TARGET >=88 and <=92	>92 and <=95	>95
3	6720.5	17.2	4.5	21.2	13.2	44.0
8	171.3	6.2	14.8	54.5	10.1	14.3
11	3631.9	8.7	3.7	24.0	11.7	51.9
12	6048.0	16.6	7.8	35.6	13.9	26.0
13	678.9	5.7	5.5	40.1	10.8	37.9
14	9995.1	12.4	5.7	29.2	12.9	39.9
15	377.5	0.5	0.1	0.8	1.9	96.7
16	6895.6	16.8	6.9	36.6	11.1	28.6
18	2665.1	15.1	4.7	28.1	11.7	40.4
22	9774.1	14.6	6.0	29.7	11.2	38.6
Total	**46958**	**14.4**	**5.8**	**29.6**	**12.2**	**38.0**

From: Poole, W. Kenneth
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; wrich@ucsd.edu; nfiner@ucsd.edu
Cc: Hastings, Betty J.
Subject: SUPPORT
Date: Wednesday, July 20, 2005 12:30:55 PM

FYI.

The 92 support babies in the data base are distributed 25, 22, 22 and 23 among the four treatment groups.

From: Poole, W. Kenneth
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP forms
Date: Wednesday, July 20, 2005 9:23:37 AM

I have no problem but what about HIPAA?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, July 20, 2005 9:08 AM
To: Poole, W. Kenneth; Das, Abhik; David Stevenson (dstevenson@stanford.edu)
Subject: FW: ROP forms

HI,
We have a "data issue" that I would like input for – the SUPPORT Trial is moving along and we need to be absolutely sure we have reliable and accurate ROP outcomes (some of these will be added after discharge). Dale has been extremely helpful with the ROP forms, but we need to insure that the ROP outcome is accurate. IN order to do this, the subcommittee thought it would be helpful if Dale could review the data forms. As this is a "data access issue" and investigators are usually NOT privy to non-site data during an ongoing trial so we were going to have Dale review the Rochester forms. However, Rochester may be most skilled in collecting this type of data due to there past experience with multiple ROP trials. So, the real question is "Should we allow Dale to review forms from other sites?" in order to write an accurate algorithm for the ROP outcome for the study?

Let me know your thoughts.

Thanks
Rose

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, July 19, 2005 5:31 PM
To: 'Hastings, Betty J.'
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP forms

Hmmmm,
I don't think so, because:

1) If we had gotten started earlier, it would be an ok plan, but we have not yet enrolled our first infant (one consented!)

2) My center already is skilled at follow up of ROP and therefore not representative of the centers that will have trouble.

Dale

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Tuesday, July 19, 2005 4:26 PM
To: Phelps, Dale
Subject: RE: ROP forms

Hi Dale,

Rose had briefly discussed this on the last SUPPORT conference call. The suggestion was that, if

possible, you should first review some of he forms that are being completed at your site first and then we can proceed from there. How does that sound?
Thanks.
Betty

-----Original Message-----
From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, July 19, 2005 2:54 PM
To: Hastings, Betty J.
Subject: ROP forms

Hi Betty,
Now that the dust is settling down around the grant renewals, may I ask about where we are with ROP forms for SUPPORT ?

Dale

From:	Neil Finer
To:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Subject:	FW: SUPPORT time in target range
Date:	Monday, July 18, 2005 3:18:42 PM
Attachments:	Time in range for supp O2 7-13-05.rtf Time in range for all 7-13-05.rtf

Hi Everyone
I'm sure your bored to death this week with nothing to do – so here are the reports – Things are looking better, and we appear to be in the range of 85-95% about 60% of the time when the infants are on oxygen. I don't yet know how many infants this represents, but you can see that this report largely reflects the activities of 4 centers –Alabama, Houston, Brown and UCSD. Overall there is 26% of the time > 95% and 13% below 85%.
We should be approaching 100 infants, and Wally is going to look at the first 200.
We will discuss at the next conference call.
Be well
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, July 18, 2005 10:15 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu
Cc: Poole, W. Kenneth; Das, Abhik
Subject: SUPPORT time in target range

Attached are updated tables for the SUPPORT pulse oximeter data time in target range.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone (919) 485-7780
Fax (919) 485-7762
mgantz@rti.org

-----Original Message-----
From: Gantz, Marie
Sent: Friday, June 24, 2005 12:09 PM
To: 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'
Cc: Poole, W. Kenneth; Das, Abhik
Subject: RE: SUPPORT time in target range

Attached are updated tables for the pulse oximeter data time in target range. If you would like an update of the gap analysis as well, I can get that to you next week (just let me know). Please let me know how often you would like to receive these updates. Every two weeks?

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
P.O. Box 12194
Research Triangle Park, NC 27709-2194

Telephone (919) 485-7780
Fax (919) 485-7762
mgantz@rti.org

-----Original Message-----
From: Gantz, Marie
Sent: Thursday, June 02, 2005 4:47 PM
To: 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'
Cc: Poole, W. Kenneth
Subject: RE: SUPPORT time in target range

Hi Neil and Wade,

Attached are two documents showing the proportion of time patients are kept in the target pulse ox ranges at each center. The low and high cases are grouped together. In one document, the numbers are based on all the available pulse ox data. In the other, the numbers are only for days on which we know the babies spent time on supplemental O2. This determination is made using information from form SUPP05. If the baby was intubated/CPAP for >8 hours on a given day and the FiO2 value at 8:00, 16:00 or 23:59 was >.21 or if the baby was on cannula/hood for >8 on that day and FiO2 recorded closest to noon was >.21, then the baby was determined to be on supplemental O2 for that day.

As you will see, we could not identify many records corresponding to days spent on supplemental O2. There are a couple of reasons for this: (1) we have not received forms SUPP05 from some of the centers, (2) we only have information about supplemental O2 for the first 14 days of life, so pulse ox data for days 15 and higher are not included.

Please let me know if you have any questions.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone (919) 485-7780
Fax (919) 485-7762
mgantz@rti.org

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, May 24, 2005 5:38 PM
To: Gantz, Marie
Subject: RE: SUPPORT time in target range

Hello Marie
Many thanks for this data. I will circulate to the Subcommittee first and then decide how to best share with the sites.
Regards
Neil Finer

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, May 24, 2005 2:03 PM
To: wrich@ucsd.edu; nfiner@ucsd.edu
Cc: Poole, W. Kenneth
Subject: SUPPORT time in target range

Neil and Wade,

Attached is a document showing the percent of time babies in the SUPPORT trial have been kept in the target SpO2 ranges. Separate percentages were calculated for the low and high SpO2 arms and for each center. Please note that these are the oximeter display values, not the actual SpO2 values. Also, note that the numbers are based on a very small number of babies. The tables include the number of babies and total number of hours of SpO2 data that went into calculating the percentages. The percent of time in each range is the overall percent of time babies at the center were kept in the range, as opposed to the average percent of time each baby was kept in the range. In other words, babies for whom more data were collected (over a longer period of time) are more heavily weighted in the percent calculations. If you have any questions regarding how these numbers were calculated, please let me know.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone (919) 485-7780
Fax (919) 485-7762
mgantz@rti.org

PERCENT OF TIME SPENT IN EACH RANGE (OXIMETER DISPLAY)
DAYS ON SUPPLEMENTAL 02 (STUDY DAYS 1-14 ONLY)

				TARGET		
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13	166.9	5.2	6.2	46.8	11.4	30.4
14	2123.6	13.2	6.2	38.6	17.4	24.5
15	1.8	11.6	0.9	5.4	13.0	69.1
16	1396.9	13.6	7.7	48.7	12.7	17.3
18	32.1	10.0	2.2	12.8	3.2	71.9
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Total	**7148.3**	**13.3**	**6.4**	**39.2**	**15.3**	**25.9**

PERCENT OF TIME SPENT IN EACH RANGE (OXIMETER DISPLAY)
ALL DATA

Center Number	Total number of hours	<85	>=85 and <88	TARGET >=88 and <=92	>92 and <=95	>95
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14	9995.1	12.4	5.7	29.2	12.9	39.9
15	377.5	0.5	0.1	0.8	1.9	96.7
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18	2665.1	15.1	4.7	28.1	11.7	40.4
22	9774.1	14.6	6.0	29.7	11.2	38.6
Total	**46958**	**14.4**	**5.8**	**29.6**	**12.2**	**38.0**

From: Neil Finer
To: "Walid Salhab"
Cc: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Subject: RE: Re SUPPORT
Date: Friday, July 15, 2005 8:03:09 PM

Hi Walid
This is great news
I hope this little girl does well.
You are well started.
Let me know if you have any issues.
Congratulations
Neil

-----Original Message-----
From: Walid Salhab [mailto:Walid.Salhab@UTSouthwestern.edu]
Sent: Friday, July 15, 2005 4:22 PM
To: higginsr@mail.nih.gov; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Subject: Re SUPPORT

Hello Neil, Wally and Rose,
Our first SUPPORT infant was born (b) (6) . A 246/7 weeks (b) (6) received a complete course of ANS, delivered by C-Section for complete cervical dilation. Randomized to early NCPAP and orange. Did very well in the delivery room. She required few breath from the Neopuff than was placed on nasal prongs CPAP with a peep valve in the delivery room and baby did well. she came to the NICU on nasal prongs CPAP. I just left the NICU and she was (b) (6) NCPAP 30% on the orange Massimo with a PaCO2 of 37. All went well in the delivery room. The NICU team is comfortable with the study and hopefully there will be no unforseen problems. I will call if we have any issues. Five ladies are on the high risk floor and have been consented.
Walid

Walid A. Salhab, M.D.
Assistant Professor of Pediatrics
Division of Neonatal-Perinatal Medicine
University of Texas, Southwestern Medical School
5323 Harry Hines Blvd
Dallas, TX 75390-9063

Phone: (214) 648-3753
Fax: (214) 648-2481
email: Walid.Salhab@UTsouthwestern.edu

From:	Higgins, Rosemary (NIH/NICHD)
To:	Petrie, Carolyn; adusick@iupui.edu; ldrichar@iupui.edu; Melody B Lohmeyer; yvaucher@ucsd.edu; mgfuller@ucsd.edu; lnoel@wihri.org; Betty Vohr; "Vivien Phillips " (E-mail); diane_hust@urmc.rochester.edu; Jensen, Rosemary; reverett@med.miami.edu; Bauer, Charles R; Neri, Maria; scosby@peds.uab.edu; ira_adams-chapman@oz.ped.emory.edu; Ellen Hale; rdillard@wfubmc.edu; npeters@wfubmc.edu; Barbara Jackson; steichjj@email.uc.edu; Elaine Romano; jlua@med.wayne.edu; ae5357@wayne.edu; Kennedy, Deborah; srhintz@stanford.edu; mbball@leland.stanford.edu; Roy Heyne; JANET MORGAN; Das, Abhik; Newman, Jamie; McClure, Beth; Alice.J.Reardon@uth.tmc.edu; bss5@cwru.edu; patricia.w.evans@uth.tmc.edu; maegan.c.currence@uth.tmc.edu; Myrna.chavarria@uth.tmc.edu; mary.j.brunner@UC.Edu; Joyce Rose
Subject:	RE: Follow Up Training materials
Date:	Friday, July 15, 2005 10:54:00 AM
Attachments:	SUPPORT Follow-on Study Revised 7-10 (2).doc Follow On Consent (2).doc Appendix C (2).doc Appendix A (2).doc Appendix B (2).doc Additional Comments (2).doc

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Here are the materials for the pulmonary follow up secondary study to SUPPORT. Please bring these items to the meeting.

Thanks
Rose

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Wednesday, July 13, 2005 5:01 PM
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Subject: RE: Follow Up Training materials

Please find the correct version of the NF11 (vs. 6_14_05)

Dear Follow Up Training Participants—

In this email I have attached the following draft **Follow Up forms** with version date.

1) NF00 (vs. 7-13-05)
2) NF01 (vs. 7-13-05)
3) NF03 (vs. 7-13-05)
4) NF04 (vs. 7-11-05)
5) NF04A (vs. 7-11-05)
6) NF05 (vs. 7-11-05)
7) NF05A (vs. 7-11-05)
8) NF10 (vs. 4-26-05)
9) NF11 ~~(vs. 5-11-05)~~ vs. 6_14_05
10) NF12 (vs. 5-11-05)
11) NF13 (vs. 2-18-03) current version

1)

Please note: I will be out of the office this Thursday, Friday and Monday. If you

have any questions or problems, please contact Dr. Higgins higginsr@mail.nih.gov or Beth McClure mcclure@rti.org.

Carolyn Petrie

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NICHD SUPPORT Trial Follow-on Study of Pulmonary Outcomes

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Proposal Updated: July 10, 2005

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A. ABSTRACT

Statement of Problem Premature infants have a greater risk for recurrent wheezing, chronic cough and more need for pulmonary care in early childhood than term infants (1-11). Although Chronic Lung Disease (CLD) is a risk factor, the etiology of symptomatic airway dysfunction, defined hereafter as recurrent wheezing and/or chronic cough, in formerly premature infants is not known.

Hypotheses The goal of this clinical project is to understand better the antecedents of symptomatic airway dysfunction among preterm infants during early childhood by evaluating the effect of treatment with different levels of targeted oxygen saturation in the immediate neonatal period. **The overarching hypothesis is that premature infants exposed to supplemental oxygen suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction and respiratory symptoms when challenged with subsequent environmental or infectious exposures.**

Hypothesis #1- Relative to infants managed with a higher SpO2 range, infants who are managed with a lower targeted SpO2 range will have less symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' corrected age (CA), whether they develop CLD or not.

Hypothesis #2- Relative to infants managed with prophylactic surfactant and conventional ventilation, infants who are managed with the early use of CPAP and a permissive ventilator strategy will have less symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' CA, whether they develop CLD or not.

Design
Longitudinal follow-up of infants enrolled in the SUPPORT Trial to determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care in the first 18-22 months' CA.

Definition of outcomes:

A) Parental Report Symptomatic Airway Dysfunction Defined as Recurrent Wheezing or Chronic Cough
B) Physician Diagnosed Wheezing or Chronic Cough.
C) Volume of Outpatient Pulmonary Care including number of pulmonary medications, office and emergency room visits and re-hospitalizations for respiratory illnesses.

Ascertainment of outcomes:

Outcomes will be measured at 4 time points in the first 18-22 months' CA as follows:

1. NICU discharge -baseline interview at to obtain family and environmental history
2. Six months' CA - telephone interview to ascertain incidence of symptomatic airway dysfunction and obtain interval history of need for pulmonary care.
3. Twelve months' CA - telephone interview as at 6 months'
4. 18-22 months' CA- Prior to the NICHD follow-up clinic visit, a telephone interview will be conducted to ascertain incidence of symptomatic airway dysfunction and obtain history of need for pulmonary care.

Anticipated Results
We anticipate that, for infants who develop CLD and those who do not, treatment with a lower vs. higher targeted oxygen saturation range will have less symptomatic airway dysfunction and less need for outpatient pulmonary care in the first 18-22 months' CA. We also anticipate that greater use of CPAP compared with conventional management will be associated with less symptomatic airway dysfunction.

Benefits and Risks
The proposed SUPPORT Follow-on Pulmonary Outcome Study will directly measure symptomatic airway dysfunction and outpatient pulmonary morbidity in infants treated with either a higher vs. lower targeted oxygen saturation. These data will provide important insight into the effect of different levels of supplemental oxygen exposure on airway growth and development in formerly premature infants. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the neurodevelopmental follow up visit. We anticipate no risk to patients enrolled in this observational follow-on study.

B. STATEMENT OF THE PROBLEM

Premature infants have a greater risk for recurrent wheezing, chronic cough and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor, the etiology of symptomatic airway dysfunction, defined hereafter as recurrent wheezing and/or chronic cough, in formerly premature infants is not known.

C. HYPOTHESES

The overarching hypothesis is that premature infants exposed to supplemental oxygen and, to a lesser extent, mechanical ventilation, in the neonatal period suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction, respiratory symptoms and need for pulmonary care when challenged with subsequent environmental or infectious exposures.

Specific Hypotheses:

Hypothesis #1- We hypothesize that relative to infants managed with a higher SpO2 range, infants managed with a lower SpO2 range will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care at 18-22 months' CA.

Hypothesis #2- We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

Hypothesis #3- We hypothesize that **among infants with CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

Hypothesis #4- We hypothesize that **among infants without CLD**, infants managed with early use of CPAP and permissive ventilator strategy relative to infants managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

D. SPECIFIC AIMS

The goal of this project is to understand better the etiology of symptomatic airway dysfunction among formerly premature infants during early childhood by examining the interaction of oxygen exposure (targeted SpO2 range), surfactant therapy and early nasal CPAP in the newborn period.

SA#1 - Measure the effect of lower vs. higher targeted SpO2 on the incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care among infants born $24^{0/7}$ - $27^{6/7}$ weeks' gestation during the first 18-22 months' CA.

SA#2 - Measure the effect of early CPAP and permissive ventilator strategy compared with prophylactic surfactant and traditional ventilator strategy on the incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care among infants born 24-27 weeks' gestation during the first 18-22 months' CA.

SA#3 – Among infants who develop CLD, determine whether CLD is milder in infants managed with low compared with high targeted SpO2 by measuring incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

SA#4 – Among infants who do not develop CLD, determine whether pulmonary outcome is better for infants managed with a low compared with high targeted SpO2 range by measuring incidence of symptomatic airway dysfunction and need for outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial

ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

E. RATIONALE/JUSTIFICATION

Although synergy in producing airway injury may exist between oxygen toxicity and mechanical forces applied to the lung, animal and human data suggest that exposure to high concentrations of supplemental oxygen alone is sufficient to cause airway narrowing and greater airway dysfunction when exposed to subsequent environmental or infectious challenges. Understanding the relative contributions of oxygen toxicity and mechanical forces on airway growth and development may facilitate development of targeted therapies for preventing or reducing symptomatic airway dysfunction in premature infants.

Why measure symptomatic airway dysfunction and outpatient pulmonary care as an outcome from a clinical NICU interventional trial?

1) Important information will be available on the effect of oxidant gas exposure on airway development and later symptomatic airway dysfunction. Exposure to oxidant gas has been causally linked with later wheezing. Existing data on the relationship between supplemental oxygen therapy and wheezing come from longitudinal cohort studies, a design that suffers from intrinsic limitations that make controlling for potential confounders of respiratory outcome difficult. By randomizing infants to higher vs. lower target saturation ranges, and thereby presumably higher or lower concentrations of inspired oxygen, *the SUPPORT Trial creates a unique, and perhaps the only, opportunity to evaluate the effect of different levels of supplemental oxygen on subsequent symptomatic airway dysfunction and need for outpatient pulmonary care after NICU discharge.*
2) Using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care can be directly quantified, allowing assessment of whether infants both with and without CLD have improved pulmonary health as a result of the study intervention.
3) The incidence of CLD, defined as an oxygen requirement at 36 weeks' PMA, is an incomplete measure of pulmonary outcome in formerly premature infants during early infancy. CLD as defined above reflects alveolar gas diffusion and NICU oxygen needs. However, outpatient pulmonary morbidity for formerly premature infants is often airway related, involving wheezing either as a primary symptom such as bronchiolitis or as a complicating symptom of lower respiratory tract infection such as pneumonia. The studies proposed here will directly measure the effect of a randomized NICU-based clinical intervention on symptomatic airway dysfunction and outpatient pulmonary morbidity.
4) The risk of a negative trial is reduced. Because the diagnosis of CLD does not completely predict need for outpatient pulmonary care, clinically significant improvements in pulmonary morbidity may occur with minimal or no change in the incidence of CLD. This result has occurred in other interventional trials in which no difference in CLD were observed (12).
5) At present, there is no standard way to measure symptomatic airway dysfunction in premature infants in NICHD pulmonary intervention trials. There is need for a better measure to assess clinical pulmonary outcome to recognize and promote therapies that reduce need for outpatient care of former extremely premature infants.

F. BACKGROUND / PREVIOUS STUDIES

Recurrent Wheezing In Preterm Infants is a Significant Public Health Problem

Outpatient pulmonary morbidity, especially recurrent wheezing and need for outpatient pulmonary care, is an understudied but clinically important outcome measure for former premature infants with and without CLD. Infants born weighing < 1500 grams (very low birth weight, VLBW) and especially infants born weighing < 1000 grams are at increased risk for small airway narrowing, airway hyperreactivity, wheezing, and nighttime cough (1-11). Up to 30-40% of formerly extremely premature infants have episodes of wheezing after NICU discharge with many requiring bronchodilators and frequent health care visits. Up to 40-50% of premature infants require

re-hospitalization, mostly for treatment of respiratory illnesses (9;12;13). In analysis of cross sectional data from the National Maternal Infant Health Survey and 1991 Longitudinal Follow up Survey, the prevalence of asthma-like recurrent wheezing varied markedly with birth weight. Infants with normal birth weight (NBW, > 2500 grams) had a 6.7% prevalence of asthma compared to 10.9% of low birth weight infants (LBW, 1500-2499 grams) and 21.9% for VLBW (14). Mean per capita asthma related costs have been estimated to be 5 times greater for VLBW compared with NBW infants. The net effect is that VLBW infants, who comprise 2% of asthma patients, consume up to 7% of asthma-related therapy costs (14).

Animal Studies

Animal studies suggest that exposure of the premature lung to hyperoxia (without concomitant mechanical ventilation) for relatively brief periods is sufficient to cause airway remodeling and smooth muscle changes that predispose toward airway narrowing and hyperreactivity to subsequent environmental challenges (15-18). In a rhesus monkey model of asthma, Schlegle et al. exposed infant monkeys to repeated cycles of inhaled House Dust Mite Allergen (HDMA), ozone or filtered air. While repeated exposure to either ozone or HDMA had mild effects, exposure to cycles of ozone followed by HDMA resulted in asthma like changes with significant increases in serum IgE, serum histamine, peripheral eosinophilia and greater airway reactivity. Using supplemental oxygen rather than the stronger oxidant ozone, Schulman et al. found that exposure of newborn guinea pigs to 70% oxygen for 96 hours resulted in airway hyperreactivity at 2 and 9 days after the cessation of oxygen. In cell models, intracellular glutathione buffers airway cells against oxidant injury during hyperoxia (19;20). Although the critical period for lung development is comparatively brief in laboratory animals compared with human infants, the duration of hyperoxic exposure (and risk of oxygen toxicity) for treatment of neonatal lung disease may extend for much longer periods in premature infants known to be deficient in anti-oxidant systems such as intracellular glutathione.

Premature Infants <u>With CLD</u> Are At Greatest Risk For Recurrent Wheezing

Among premature infants, infants with bronchopulmonary dysplasia (BPD) are at highest risk for poor pulmonary outcome after NICU discharge. Infants with CLD have small airway compromise with decreased forced expiratory flow velocities, airway hyperreactivity, and increased functional residual volume suggesting airway obstruction (2;5;9;21-24). In a pulmonary follow up of infants with RDS or BPD, De Klein et al. found infants with BPD had reduced FEV1 at baseline while infants with RDS but not BPD had significant improvements in FEV1 following bronchodilator therapy. In this study, a history of recurrent wheezing predicted abnormal pulmonary function (25). In a recent study of infants with CLD, Robin et al. found that 50% of infants with CLD had symptoms of recurrent wheezing and 35% showed significant airway responsiveness to bronchodilators, evidenced by a 24% increase in forced expiratory flow velocity at 75% of expired forced vital capacity (FEF_{75}). This study demonstrated the relationship between recurrent wheezing as a clinical symptom and the physiologic measurement of airway obstruction. Infants with CLD and a history of recurrent wheezing showed greater hyperinflation, expiratory flow limitation and airway responsiveness to albuterol compared to those without a history of recurrent wheezing (24).

Premature Infants <u>Without CLD</u> Have Significant Airway Dysfunction

Among VLBW infants who do not develop CLD, several studies of pulmonary outcome have found an association between neonatal oxygen exposure and increased prevalence of expiratory flow dysfunction and airway hyperreactivity (4;11;26-29). Some authors attribute reductions in airway function to intrinsically small airways as a consequence of poor intrauterine growth rather than superimposed airway injury or reactivity from neonatal respiratory disease (1;30). However, because small airways alone do not fully explain airway hyperreactivity, other mechanisms of small airway dysfunction are necessary to explain respiratory symptoms.

Several pulmonary outcome studies have reported significant increases (2-fold or more) in airway obstruction among VLBW infants without CLD following exposure to as little as 40% oxygen for 5 days (3;4;8;26). Not all studies have had similar results suggesting variability in effect or susceptibility of babies to oxygen exposure (31;32). In 1982, Coates et al. described increased small airway resistance at 10 year follow up of mildly

premature infants (mean gestational age 31 weeks and birth weight 2000 grams) treated with a high oxygen (O2) regimen and those exposed to a low O2 regimen for the treatment of respiratory distress syndrome (RDS). Mechanical ventilation was not used in either group. Pulmonary function tests were performed on survivors receiving either the low or high supplemental oxygen regimen ten years after their initial illness. Infants treated with high levels of supplemental oxygen alone (no mechanical ventilation) had decrements in airway function similar to decrements in function reported for a historical cohort of RDS survivors treated with ventilation and high levels of supplemental oxygen. From these data, the authors concluded that neonatal exposure to high oxygen concentrations in the absence of mechanical ventilation is capable of causing long-term change in small airways (28). These studies suggest that use of lower supplemental oxygen concentration may improve respiratory health of infants who do not develop CLD.

Premature Infants Without CLD Have Increased Risk of Symptomatic Airway Dysfunction and Need for Outpatient Pulmonary Care.

For VLBW infants without CLD, the prevalence of parental or physician reported wheezing is increased compared with term infants, with estimates of the prevalence of wheezing ranging from 10-38% (4;8). Prevalence of wheezing requiring medications is greater compared with term infants. VLBW infants have a 2-4-fold increase in respiratory related re-hospitalization rates compared with term infants (4;8;33-35). Although most studies have found the risk of recurrent wheezing remains elevated throughout childhood, an Australian longitudinal follow-up cohort of VLBW infants found the prevalence of wheezing remained elevated for 2 years then returned to baseline (32;36).

Prevalence of Symptomatic Airway Dysfunction in Formerly Preterm Infants During the Surfactant Era Remains High

With the advent of surfactant therapy, survival of small infants increased dramatically and the incidence of CLD changed minimally (37-40). Classic BPD evolved into the "new CLD" characterized by reduced alveolarization and more variable airway changes (41). Pulmonary follow up studies during the surfactant era showed reduced pulmonary morbidity in surfactant treated patients. Typical of these studies, Sell et al. found the incidence of asthma was significantly lower in infants given synthetic surfactant compared with those given air placebo. Pelkonen et al. performed PFT measurements on 40 children aged 7-12 years who were born before 30 weeks of gestation with an immature surfactant system, and were randomized to one of three treatment groups: prophylactic surfactant, rescue surfactant and placebo (air). Spirometric parameters of preterm born children were compared with those of 20 children born at term. Bronchial obstruction was found in 53% of the prophylactically treated group, in 36% of the rescue group, in 67% of the placebo group, and in 0% of the control group (42). A recent report suggests that the introduction of surfactant therapy markedly altered the pulmonary outcome of premature infants. Published in 2001, the Newborn Lung Function Project Group reported results of a prospective 12-year follow-up of VLBW infants following the introduction of surfactant therapy (5;8;43). Among infants with CLD, wheezing symptoms decreased from 50 to 16% from the period before compared with the period after surfactant therapy became available. However, among infants without CLD the prevalence of wheezing increased from 14% to 38% with the introduction of surfactant. These data suggest that surfactant therapy has an effect on outpatient respiratory health and underscores the need to consider outpatient pulmonary outcomes in evaluating therapeutic strategies that potentially decrease surfactant replacement therapy.

CLD is an Incomplete Predictor of Outpatient Pulmonary Morbidity

Several authors have looked to respiratory symptoms and need for outpatient pulmonary care as outcome measures for neonatal lung disease (9;10;12;24). In 1988, from a retrospective chart review of 605 premature infants < 1500 grams, Shennan et al. found that the presence of BPD (oxygen requirement at 36 weeks PMA) had a 63% positive predictive value and a 90% negative predictive value for abnormal pulmonary outcome in the first 2 years of age. However, this study from before the era of exogenous surfactant therapy defined abnormal pulmonary outcome as death, oxygen requirement at 40 weeks PMA, 2 or more respiratory related hospital admissions, wheezing requiring drug therapy or persistent wheezing resulting in growth failure, handicap or hypotonia at 1 year of age. Such restrictive criteria for abnormal pulmonary outcome are likely to

underestimate the burden of recurrent wheezing on former premature infants and their families. Several recent interventional studies show that CLD is an incomplete predictor of clinical wheezing and need for outpatient pulmonary care and suggest that differences in oxygen exposure or oxidant stress may affect pulmonary outcome without affecting the incidence of CLD.

Interventional Trials That Did Not Reduce CLD But Did Reduce Outpatient Pulmonary Morbidity.

Recent data in preterm infants treated with human recombinant superoxide dismutase (SOD) found that anti-oxidant therapy did not reduce the incidence of CLD. However, among infants < 27 weeks gestation SOD therapy resulted in significant reductions in the first year after NICU discharge in the number of emergency room visits and number of re-hospitalizations for respiratory problems and reductions in the need for bronchodilators suggesting a reduced prevalence of wheezing in patients treated with SOD (12). In a randomized, multi-center trial from Helsinki, N acetyl cysteine did not reduce the incidence of CLD. Outpatient pulmonary outcome of these patients has not been reported.

Treatment of Premature Infants With Higher Targeted Oxygen Saturations Is Associated with Poorer Pulmonary Outcome

In the STOP-ROP Study, infants exposed to higher levels of oxygen to achieve a targeted saturation of 96-99% compared with 89-94% had greater risk of adverse pulmonary events including pneumonia, chronic lung disease exacerbations and need for diuretics, oxygen and hospitalization at 3 months" corrected age. *Although all infants in this study had CLD at enrollment, different targeted oxygen saturation were associated with large differences in pulmonary morbidity.* Adverse pulmonary outcomes occurred with differences in FIO2 of as little as 10% for patients treated with ventilation, CPAP or hood (36% $\pm$ 14% vs. 46% $\pm$ 20%, respectively for low vs. high saturation range) and 5% for infants treated with nasal cannula, (26% $\pm$ 6% vs. 31% $\pm$ 11%, respectively for low vs. high saturation range) (44). In a similar study, The Benefits of Oxygen Saturation Targeting (BOOST) Trial randomized infants < 30 weeks' gestation to higher (95-98%) or lower (91-94%) saturations ranges beginning at 32 weeks' PMA to determine whether infants managed with higher targeted saturation range showed better growth and neurodevelopment. As in the STOP-ROP study, need for oxygen therapy was prolonged. Trends towards an increased risk of pulmonary death and fewer outpatient office visits (median 27.5 vs. 31.3, $p < .11$) were seen in the lower targeted oxygen saturation group (13).

Factors In Addition To Prematurity and Oxygen Contribute To Symptomatic Airway Dysfunction

Multiple factors in addition to prematurity and oxygen contribute to the development of airway dysfunction in children (Table 1). In the SUPPORT TRIAL Pulmonary Outcomes Follow on Study, these potential covariates will be measured and controlled for using a randomized trial design. These covariates will be also be evaluated as independent predictors of pulmonary outcome in multivariate analyses.

Table 1. ***Important Covariates in Etiology of Recurrent Wheezing***

Demographcis – race, sex, ethnicity, parental factors (educational level, poverty status, and age), and family history of wheezing or atopy.

Environmental – urban vs. rural residence, presence of dust, tobacco smoke or wood smoke in the home, pets

Health Services – adherence to medications, availability of level of health care

Medical- gastroesophageal reflux, congenital anatomic airway abnormalities, RSV and other viral infections

G. METHOD/ PROCEDURES

NICHD SUPPORT Trial Follow-on Study of Pulmonary Outcomes

G.1 Description of study design

This study will add an 18-22 month longitudinal, prospective follow-on study of surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial.

G.2 Definition of study population

Infants with gestational age of $24^{0/7}$-$27^{6/7}$ weeks' gestation by best obstetrical estimate.

Inclusion criteria:

- Full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Parents/legal guardians have provided consent for enrollment
- No known major congenital malformations
- Survival to hospital discharge

Exclusion criteria

- Transport to the center after delivery
- Research apparatus/study personnel are not available.

G.3 Description of study intervention

Before delivery, infants will be randomized to subsequent management with high vs. low target oxygen saturation according to the SUPPORT Protocol. The SUPPORT Follow-on Study of Pulmonary Outcomes begins just prior to NICU discharge (Figure 1).

Figure 1. **SUPPORT Trial Follow-on Study**

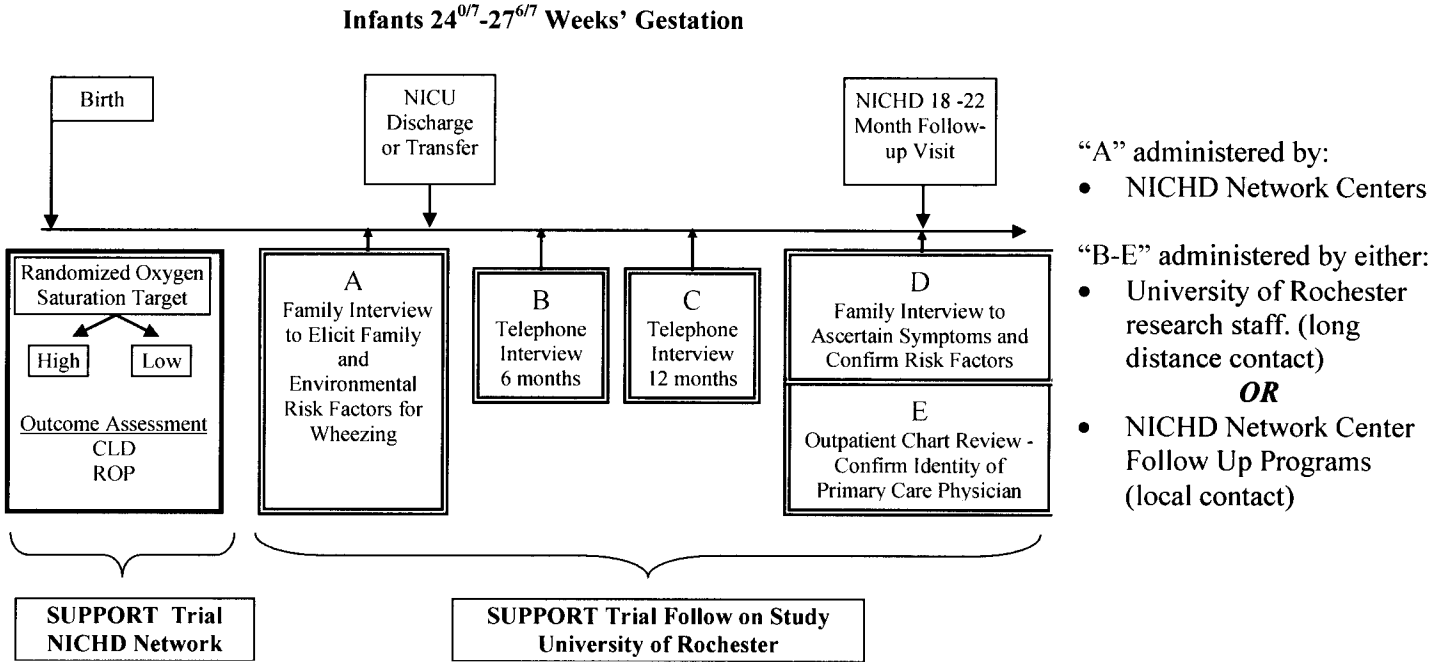

Fig 1, A. Parent (Guardian) Interview to Elicit Family and Environmental Risk Factors for Wheezing and Cough
The family interview will be administered at each participating Network Center by site study nurses

prior to NICU discharge or transfer. The questions are based on intake questions used by the Tucson Respiratory Study and are designed to elicit family history of asthma, atopy, and home environment and to identify likely care givers (Questionnaire, Appendix A). Consent for release of medical information will be obtained to facilitate contacting physician offices to obtain office data.

Fig 1, B. Telephone Interview at 6 months PMA – respiratory interval history

Fig 1, C. Telephone Interview at 12 months PMA – respiratory interval history

Telephone interviews will be undertaken at 6 and 12 months to obtain limited interval history of respiratory problems including wheezing, cough, medications used, and health services sought for respiratory related problems (Questionnaire, Appendix B).

Fig 1, D. Parental Interview to Ascertain Incidence of Wheezing and Cough and Confirm Risk Factors- This parent interview will also be administered by telephone, prior to the regularly scheduled 18-22 month NICHD developmental follow up clinic visit. Contacting parents prior to the office visit will help improve the Developmental Follow Up Clinic attendance rate and will allow the clinic visit to provide a back up means to contact the family. Telephone interviews, the 2 limited telephone interviews and the second family history interview at 18-22 months, will be conducted either by the local NICHD Follow Up Program or long distance from Rochester, based on center preference (see table 2 below). The interview questionnaires are based on questionnaires administered by the Tucson Respiratory Study at approximately one year of age (Questionnaire, Appendix C). Questions are designed to ascertain the frequency and severity of wheezing and cough episodes. In addition, risk factors obtained at the 1st interview will be confirmed.

In an effort to help standardize the interview, a training program will be provided to train local interviewers on a standard approach to administering the questionnaires.

Fig 1, E. Outpatient Chart Review - Confirm Identity of Primary Care Physician

To confirm results of physician report of wheezing obtained by telephone interview, patients undergoing telephone interview will have their primary care physician's medical record reviewed.

E.1 – Physician report of recurrent wheezing and chronic cough

E.2 – Frequency of outpatient pulmonary care. The volume of outpatient pulmonary care including, outpatient primary care physician office visits, pulmonary specialty care, emergency room visits, hospitalizations and the number and duration of pulmonary medications will be obtained from primary care physician chart review mailed from and returned to each local Center. To incentivize primary care office staff to complete the chart review, a $25 honorarium will be offered for successful completion of the chart review form (45-47).

Table 2. SUPPORT Trial - Pulmonary Outcomes Study

NICHD Site	*6, 12 and 18-22 Month Pulmonary Questionnaires Administered By*
Alabama	Alabama
Brown	Brown
Cincinnati	Rochester
CWRU	CWRU
Dallas	Dallas
Duke	Duke
Emory	Rochester
Houston	Rochester
Indiana	Rochester
Miami	Miami
Rochester	Rochester
Stanford	Rochester
UCSD	UCSD
Wake Forest	Wake Forest
Wayne State	Wayne State
Yale	Yale

G.4 Precise definition of co primary/secondary outcomes

G.4.1 Definition of primary outcomes- parental report of recurrent wheezing and chronic cough.

Two primary outcomes will be measured, the incidence of recurrent wheezing and incidence of chronic cough. Whether individual symptoms (recurrent wheezing or chronic cough, alone) or a combination of these symptoms (wheezing and/or chronic cough, together) best quantifies symptomatic airway dysfunction following premature birth is controversial. Many studies have used wheezing alone as a primary outcome measuring pulmonary morbidity in formerly premature infants (10;12;14;48). In 1996, Greenough, using a combined outcome of either wheezing or chronic cough as a measure of symptomatic airway dysfunction, found that greater pulmonary symptoms were associated with longer durations of supplemental oxygen and mechanical ventilation (49;50). Later, in a follow-up study of infants enrolled, The United Kingdom Oscillator Study (UKOS), Greenough found that frequent wheezing episodes but not chronic cough were associated with neonatal respiratory events (51;52). In our study, to address this issue most conservatively, recurrent wheezing and chronic cough will be measured as co-primary outcomes. Secondary analyses will consider these outcomes in combination.

The incidence of wheezing will be ascertained using the primary question used and validated in the Tucson Children's Respiratory Study (a large prospective birth cohort study of term infants) (53-59), "Has his/her chest ever sounded wheezy or whistling?" (53). Likewise, the incidence of cough will be ascertained using the Tucson question, "Has this child ever had a cough when he/she did not have a cold?" (53). As in Greenough's study, recurrent wheezing will be defined as episodes of wheezing occurring more than twice/week. Chronic cough will be defined similarly, cough occurring as more than twice/week. Additional questions will further characterize the wheezing and coughing episodes, including whether symptoms were associated with a viral illness (parental report of a "cold") or an environmental exposure. A symptom diary will be offered to study participants to help facilitate recall of pulmonary symptoms and need for outpatient pulmonary care.

To facilitate The Tucson Children's Respiratory Study administered the questionnaires both in person and by phone, depending on patient availability. The investigators did not undertake a formal validation of phone vs. face-to-face administration of the questionnaire. Anecdotally, based on phone conversation with the study coordinator, investigators did not observe a difference in quality of responses between phone and questionnaires administered in person.

G.4.1.1 Standard Definition of Wheezing

Several studies have found that multiple colloquialisms in both English and Spanish can be used to describe wheezing (60-64), creating opportunity for misinterpretation of respiratory sounds and potential for over or under estimation of the incidence of wheezing. Other studies have found that clips of respiratory sounds played for families improve accuracy of symptom reporting (65;66), providing data relatively free from biases due to language, culture, literacy or interviewing techniques. To minimize variation in interpretation of respiratory sounds as wheezing we will provide a verbal AND a brief audio clip that can be played for the interviewee at the beginning of the interview (electronic Appendix D). Accompanying the audio clip, wheezing will be defined verbally by the interviewer as an expiratory sound (a sound that is made when breathing out, not in) coming from the chest, sometimes described as whistling or musical. Although not yet widely used, use of audio clips to standard symptom definition is the best approach to bridge the language gap that exists between English and Spanish and among Spanish speaking populations using different dialects or colloquialisms.

In administering the questionnaires, every effort will be made to accurately measure the occurrence of pulmonary symptoms and health care and medication use, thus establishing the true incidence of pulmonary morbidity in the study population as a whole. Most importantly, however, because pulmonary morbidity is a blinded outcome measure from a randomized controlled trial, bias favoring one study arm over another should not occur.

G.4.1.2 Parental Report for Non-English Speaking Populations

Upon finalization of the questionnaires, Spanish language versions will be created and made available to all centers. The Cornell Translation Service, a University based professional translation service, will be contracted to perform the translation. For centers choosing Rochester to administer the questionnaire to their patients, English and Spanish speaking individuals, trained to administer the questionnaires, will conduct the telephone interviews. For centers choosing to administer the questionnaires locally, each center will be free to choose their primary interviewer who has the necessary skills. Administration of the questionnaire by a native speaker of the local Spanish dialect is recommended. An audio clip and verbal definition of wheezing will be presented to the respondent to standardize interpretation of wheezing and to minimize ascertainment biases due to language, culture, literacy or interviewing techniques.

G.4.1.3 Parental Report of Pulmonary Symptoms Is a Reliable Outcome Measure of Airway Dysfunction

Evaluation of frequency and severity of respiratory symptoms by parental questionnaire and need for pulmonary care has been used as the primary outcome in multiple follow up studies of term and premature infants (10;12;14;48). A recent review evaluated the value of respiratory symptom history ascertained by parental questionnaire in determining the risk for developing asthma in early childhood. By evaluating 9 large, longitudinal, full term birth cohort studies and reviewing the original questionnaire from 7 of these studies, Koopman found that the questions posed to parents eliciting a history of wheezing in their infants were similar. Parental report of wheezing predicted an increased risk for later respiratory symptoms, including asthma. In the studies proposed here, incidence of recurrent wheezing and chronic cough ascertained by parental report will be primary outcomes, rather than physiologic measurements of airway dysfunction, for several reasons.

G.4.1.4 Reasons to Use Parental Report of Recurrent Wheezing and Chronic Cough as Primary Outcomes

- Parental interview can be performed more readily on large numbers of patients. The validity of this approach has been shown in several longitudinal studies including The Tucson Respiratory Study.
- Recurrent wheezing is highly correlated with changes on pulmonary function testing (PFT). In infants with CLD, a history of wheezing was associated with greater expiratory flow limitation, hyperinflation and airway responsiveness to albuterol on PFT compared to those without such a history (24).
- Parental recall of respiratory illnesses has been shown to correlate strongly with review of medical office records. For asthma and bronchitis in the past year, Pless et al. found good agreement between recall of 288 parents and physician office chart review. Parental education and occupation were not predictive of a parent's ability to recall the illness (67). In an assessment of parental recall done to evaluate minor injury in children, Harel found recall declined with time, with the best recall occurring in the first 3 months after injury with further decline after 6 months from the time of the injury (47;68;69).
- Symptomatic airway dysfunction can be assessed in a standardized way. The NHLBI Consensus Expert report developed standardized questions to assess severity of airway dysfunction. Three standardized questions from this report will be administered at 6, 12 and 18 months to assess symptom severity (70).

G.4.2 Definition Of Physician Diagnosed Symptomatic Airway Dysfunction. Secondary outcomes will include physician report of recurrent wheezing, defined as more than 1 episode of wheezing at an office visit, or chronic cough, defined as cough not associated with a cold at more than one office visit (49;50). Physician diagnosed airway dysfunction will be collected by parental report during the telephone interviews and by review of the primary care physician's medical chart.

G.4.3 Definitions of Secondary Outcomes - Measures of Volume of Outpatient Pulmonary Care

Important secondary outcomes of outpatient pulmonary morbidity will be collected (Table 3).

Table 3. *Secondary Outcomes, Covariates and Sources*	
Outcomes	Source
Secondary Outcomes	
Number and duration of outpatient pulmonary medications including bronchodilator, diuretic, methylxanthine, and inhaled and systemic steroid therapy.	Family interview, primary care chart review
Number of office visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of emergency room visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of re-hospitalizations for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Growth at 18 months PMA (height, weight and head circumference)	NICHD follow up clinic data

G.4.4 Data Collection

G.4.4.1 Data Collection: Ascertainment of Outcomes - Field Work

A. Ascertainment of Wheezing and Outpatient Pulmonary Morbidity By Telephone Interview. There will be 4 parental interviews over 18-22 months, one prior to NICU discharge and 3 subsequent telephone interviews at 6 month intervals to collect data on recurrent wheezing, chronic cough and volume of outpatient pulmonary care (Figure 1, A-D above). Based on review of longitudinal studies of full term infants in which follow up patient contacts occurred quarterly to once every 18 months', a 6 month interval for follow up patient contacts is planned in an effort to reduce parental recall omissions which are more likely to occur with less frequent follow up (48;68). The 4 interviews are designed to collect the primary and secondary outcomes of the follow-on study. Other inpatient and outpatient data will be collected as part of the NICHD Neonatal Research Network Generic Database (GDB) and Follow-up Program.

B. Interview Instruments – (Appendices A-C) Questionnaires are based on the Tucson Children's Respiratory Study, a longitudinal cohort study that followed healthy term infants from birth to over 20 years of age. Questionnaires have been updated with validated symptom severity and tobacco smoke exposure questions, a current list of available respiratory medications and modifications that address health issues faced by formerly premature infants such as use of palivizumab for RSV prophylaxis. The original Tucson questionnaires are designed to elicit a thorough history of possible covariates, such as environmental and infectious exposures and family histories of atopy, asthma or respiratory disease.

C. Administration of Interview Instruments – Telephone interviews will be initiated in one of two ways (table 2):

C.1 University of Rochester research staff (long distance contact)

The University of Rochester Neonatology Research Group has conducted similar telephone interview designs as part of an ophthalmologic outcome study of patients enrolled in a randomized trial of cryotherapy to treat ROP and a 15-year, longitudinal neurological assessment conducted by telephone survey among 132 infants treated with surfactant. Telephone follow up rates were 96% follow up at 7 years and 95% follow up at 15 years (71). In the study proposed here, the University of Rochester Health Services Research Group (HSR Group), will conduct the telephone interviews.

In telephone follow up surveys conducted by the HSR Group, follow up rates at 12 months' have exceed 75% in populations at high risk for being lost to follow up (72-78). Working with NICHD Network Centers to assist in tracking local families, follow up rates for this Follow-On Study are expected to exceed 80% and should approach the average annual NICHD follow up rate of 83%.

To facilitate tracking and record keeping, Network Centers choosing Rochester to administer questionnaires to their patients (table 2) will provide contract information to the Rochester site. Research Triangle Institute will provide monthly updates of patients due for interviews. Local centers will be responsible to maintain updated contact information. Each interview will close with a question as to whether the family plans a new address or phone number prior to the next interview. The names and phone number of a friend or relative and their primary care physician will be sought so that they may be contacted in the event that contact with the patient is lost. If contact information is updated, the new contact information will be transmitted back to the local center. By interviewing families every 6 months', a higher follow up rate will be achieved because family contact information will not become so out of date that the family is lost or that re-contacting them is inefficient. We anticipate that each

interview will require 2 hours of staff time, with 20-30 minutes to conduct the interview and 90 minutes to contact family and enter data.

Advantages of Conducting Telephone Interviews From a Central Research Facility

Conducting the telephone interviews from Rochester will:
1) require less effort from the individual Network Centers
2) allow standardization of the telephone interview by a core group of trained interviewers
3) blind the telephone interviewer to the SUPPORT Trial study group designation
4) reduce the cost of the study by consolidating the telephone training and follow up at one site.

C.2 NICHD Network Center Follow Up Programs (local contact, Table 2)

Individual NICHD Network Centers may choose to undertake administration and tracking of patients enrolled in the SUPPORT Follow-On Study. Local administration of the telephone questionnaires capitalizes on existing NICHD resources available at local centers. Each Network Center choosing local administration of the telephone questionnaire will identify one or more telephone interviewers who will undergo training in the administration of the questionnaire and tracking of the enrolled patient. The Rochester Health Service Research Group will serve as a resource to answer questions regarding administration of the questionnaire.

Advantages of Conducting Telephone Interviews From the Local Network Centers

Conducting the telephone interviews from Local Centers will:
1) reduce risk for HIPPA violation
2) capitalize on existing rapport between the patient's family and their local center
3) avoid redundancy in making tracking calls to families

D. Physician Office Record Assessment of Wheezing, Cough and Outpatient Pulmonary Morbidity

Physician office charts will be reviewed to determine physical findings of wheezing, cough, medication use and respiratory-related hospitalizations. Consent to release medical information will be obtained at the time of study consent. As part of the 18-22 month telephone questionnaire, office contact information will be obtained from the family. For primary care pediatricians, a copy of the family's signed consent authorizing release of medical information and an office data extraction form will be mailed or faxed to the provider. The form will be based on a similar document used by the Rochester Research Group to obtain medical information on respiratory health issues. To incentivize office staff to complete the data extraction form, a $25 honorarium will be offered upon receipt of the completed form.

G.4.4.2 Data Collection: Ascertainment of Environmental and Genetic Covariates

Ascertainment of important environmental exposures and genetic risk factors that might confound the relationship between supplemental oxygen exposure and symptomatic airway dysfunction will be obtained along with the primary outcomes during the same telephone and family interviews. Tobacco smoke exposure is a potentially significant risk factor for airway dysfunction. The tobacco smoke question in the Tucson Study has been replaced by a question shown by Dr. Wakefield et al to correlate with cotinine levels in infants (79;80).

Table 4. Postnatal and Genetic Covariates Evaluated as Potential Confounders of Oxygen and Wheezing

Covariates in Home Environment and Exposures The initial questionnaire and 6 month interviews will gather information on other *inhaled exposures* (tobacco, wood stoves, cold air), *residence* (urban vs. rural residence), *infectious exposures* (RSV, palivizumab) and medical risk factors (gastroesophageal reflux, congenital anatomic airway abnormalities)

Covariates in Family History Questionnaires will elicit *family history* of atopy (family history of asthma, eczema or allergy to foods, pets, molds, pollen or dust).

G.4.4.3 Data Collection: Ascertainment of Primary Exposure

Oxygen Exposure

In the SUPPORT Trial, it is assumed that managing infants with a higher vs. lower targeted oxygen saturation range will result in different levels of supplemental oxygen exposure. The SUPPORT Trial will collect data on FIO2 exposure to quantify the anticipated difference. As part of the SUPPORT Trial, FIO2 values will be recorded and analyzed at many time points including time of admission, first blood gas, and as described in the SUPPORT Manual of Operations, Chapter 10 Safety Monitoring Form. Because oxygen is the primary exposure in the SUPPORT Follow-on Study and plays a central role in the disease model proposed, oxygen exposure will be quantified as described in the main SUPPORT trial and analyzed as a predictor of later symptomatic airway dysfunction.

G.5 Sample size estimate with some statistical support based upon primary outcome

G.5.1 Sample Size

The SUPPORT Trial anticipates enrollment of 1310 patients $\geq 24^{0/7}$ and $\leq 27^{6/7}$ weeks' gestation, providing 80% power to detect a 10% difference between treatment groups in the incidence of death/CLD and death/stage III Retinopathy of Prematurity (ROP). Assuming mortality of 22% for infants in this GA range (NICHD 2001-2002 data), 1021 infants would be expected to survive and be eligible for the SUPPORT follow-on study.

Power for detecting a difference between the high vs. low saturation groups for the primary outcome

First we consider power for detecting a difference between the high and low saturation groups for the first primary outcome, recurrent wheezing. We expect the incidence of wheezing to be about 0.17 in the low saturation group and about 0.31 in the high saturation group (12). For the power calculations, we also consider a scenario with a smaller difference between groups: 0.19 for the low saturation group and 0.29 for the high saturation group. We expect the follow up rate to be about 80% (NICHD historical average follow up rate), which would result in data on about 816 patients. We also consider a lower follow up rate of 65%, which would result in about 663 patients. Power to detect a difference between groups based on a chi-square test with type I error alpha set at 0.05 is given in Table 5 for each scenario. From those results, we expect to have more than 80% power for the primary outcome. Also of interest are subgroup analyses, where we look separately at the CLD and non-CLD subjects. Of survivors, we expect 37% or 378 infants to have CLD. For the CLD group, we expect the incidence of wheezing to be about 0.5 in the high saturation group and 0.3 in the low saturation group. If there is a 80% follow up rate, we will have 95% power to detect a difference between the two groups. For the non-CLD subgroup, we expect the incidence to be 0.2 and 0.1 in the high and low groups, respectively. With 80% follow up, we will have 92% power. Thus, we expect to have adequate power for the primary outcome even in the analyses stratified by CLD.

Table 5. Power for primary outcome.

Follow-up rate	Low Saturation	High Saturation	power
80%	0.17	0.31	0.99
80%	0.19	0.29	0.90
65%	0.17	0.31	0.98
65%	0.19	0.29	0.83

Power for detecting a difference between the high vs. low saturation groups for secondary outcomes

We expect the study to be adequately powered for analysis of important secondary outcomes such as use of pulmonary medications. Based on results reported in Davis et al. for infants less than 27 weeks' gestational age [22], we expect the rate of pulmonary medication use to be 0.42 in the high saturation group and 0.19 in the lower saturation group. In that case, even with a 65% follow up rate, we would have more than 99% power to detect a difference between the groups with a chi-square test. Similarly, the CLD subgroup analyses would have more than 80% power under those assumptions. Based on the power numbers above, we could potentially enroll fewer subjects in the trial and still have adequate power. However, we choose to over enroll slightly to make up for the fact that some patients will likely be lost to follow up. The recruitment time will be that of the SUPPORT Trial (2 years) with a run out period of 18-22 months to ascertain follow-up outcomes. The total study period is 36-40 months.

G.5.2 Data Analysis

Analysis of primary dichotomous outcomes will be performed by chi square test and presented as a relative risk for development of that outcome. Number of outpatient pulmonary visits for respiratory illnesses will be presented as median values. The Wilcoxon Rank Sum test, a non-parametric alternative to the two-sample t-test, will be used to test for differences between the two groups. Statistical analyses will need to consider the effect of multiple comparison groups on the level of statistical significance. All analyses will be performed in conjunction with the Research Triangle Institute (RTI, North Carolina), the biostatistical support group for the NICHD Neonatal Network. Data will be presented as shown in tables 5-6. Mean FIO2 values in the high and low SpO2 groups will be compared by two sample t-test. Secondary analyses will be done to evaluate the effect of ventilator strategy on pulmonary outcome and presented similarly to table 5 and 6.

Table 6. *Primary Dichotomous Outcomes*	**Low Saturation**	**High Saturation**	**RR**	**CI**	**p-value**
Parental Report of Recurrent Wheezing (%)					
Physician Diagnosed Recurrent Wheezing (%)					
Need for Outpatient Pulmonary Medications (%)					
Need for Physician Visit for Respiratory Illness (%)					
Need for Re-hospitalization for Respiratory Illness (%)					

Table 7. *Primary Outcomes – Continuous Outcomes*	**Low Saturation**	**High Saturation**	**p-value**
Number of Physician Visit for Respiratory Illness (Median)			
Number of Emergency Visits for Respiratory Illness (Median)			
Number of Re-hospitalization for Respiratory Illness (Median)			

G.5.2 Expected Results

We predict that premature infants managed with a lower targeted oxygen saturation range compared to those managed with a higher targeted oxygen saturation are exposed to lower levels of supplemental oxygen and have reduced risk of recurrent wheezing in the first 18-22 months' CA.

G.5.2 Anticipated Problems and Solutions

1) Participant attrition. As seen in the sample size calculation, the potential for patients to be lost to follow up over time will be offset by over enrolling patients to participate in the follow up. Because patients who enroll in the SUPPORT Trial are randomized, there should be no systematic bias favoring one group over another among patients who are lost to follow up. However, if loss to follow up is in part caused by the treatment or outcomes, this could bias the results. We will therefore investigate whether there are differences in key variables for subjects who are lost to follow up compared to those who remain in the study. For example, we will test whether subjects in one treatment arm were more likely to be lost to follow up than in the other arm. Similarly, we will compare wheezing rates at 6 months' for those who are later lost to follow up compared to those who remain in the study. We do not expect to see any major differences.
2) Difficulty tracking families. With mobile families, keeping contact information up to date may be difficult. To promote successful follow up in both the Pulmonary Outcome Study described here and the routine NICHD neurodevelopmental follow up visit at 18 - 22 months, each center will be responsible to track families to maintain current contact information for both the family and primary care physician.
3) Center variability in administering the questionnaire. With 11 centers administering the telephone questionnaires, variation in techniques and styles in administering the questionnaires has the potential to introduce ascertainment bias. To minimize this risk, a face-to-face training program will be conducted by he Rochester Site for all staff administering the questionnaires.
4) The SUPPORT Follow-on Study of Pulmonary Outcomes has been prepared as the central project for Dr. Stevens' Patient Oriented Clinical Research Grant (K23 Award), revised submission 7/1/05. If approved, funds from the K23 will be available to offset a portion of the cost of conducting this

SUPPORT Trial Follow-on study. If not approved, NICHD funding has been approved to support this project.

5) Initiation of the Pulmonary Outcome follow On Study after enrollment into SPPORT has begun.

5.1 Babies already enrolled in SUPPORT

To help assure pulmonary outcome assessment for all SUPPORT patients, families of babies already enrolled in SUPPORT will be approached with a separate consent to enroll in the Pulmonary Outcome Study. IRB approval of this consent form will be required.

5.2 *Future babies eligible for enrollment in SUPPORT*

Going forward, a modified SUPPORT Consent Form, which includes consent for the Pulmonary Outcome Study, will be need to be prepared at each center. The revised SUPPORT Consent will require

G.6 Available population/compatibility with other ongoing protocols

Another secondary study proposed by a group independent from ours is looking at the genetics of reactive airways disease in patients enrolled in the SUPPORT Trial. The follow on study proposed here should be complementary to the genetics study, enhancing the both the quality and quantity of data on the prevalence of wheezing and need for outpatient pulmonary care in patients enrolled in the SUPPORT Trial.

G.7 Estimate of projected recruitment time

The recruitment time will be that of the SUPPORT Trial with a 18-22 month period of follow up to ascertain primary and secondary outcomes.

H. RISKS / BENEFITS, WITH ESTIMATE OF FREQUENCY / SEVERITY OF RISKS.

By using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care may be quantified, allowing assessment of whether infants who develop CLD and those who do not have improved pulmonary health as a result of the study intervention. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the follow up visit. We anticipate no risk to the patient of this observational follow on study.

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APPENDIX B

SAMPLE CONSENT FORM

University of California, San Diego
Consent to Act as a Research Subject

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial of the NICHD Neonatal Research Network

Neil Finer, MD, his associates, and the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network are conducting a research study to find out more about treatment with CPAP (positive pressure applied with a face mask to help keep the lungs inflated) and learn the appropriate levels of oxygen saturation (oxygen levels in the blood) in premature babies. You are being asked to allow your child to be in the study because there is a possibility he/she will be born between 16 and 12 weeks early (24-28 weeks gestational age).

The purposes of this trial are the following:
1) To compare infants who receive delivery room CPAP and who have strict guidelines for having a breathing tube placed with infants who have the tube placed and surfactant (a liquid which helps babies with immature lungs breath easier by helping keep their lungs from collapsing) given in the delivery room.
2) To compare low range (85-89%) oxygen saturation levels with high range (91-95%) levels to determine if a lower range results in decreased ROP (Retinopathy of Prematurity, an eye disease that may result in impairment of vision or even blindness, which may be caused by excessive levels of oxygen.)

Duration of the Study: We expect to include about 1300 babies in the study from all the NICHD Neonatal Research Network hospitals over a two-year period.

The use of CPAP and Intubation/Surfactant are both treatments currently used in the delivery room at UCSD. The decision as to which to use is currently made by the physician attending the delivery.

The oxygen level currently used in the NICU at UCSD is between 85% and 95%. Both treatment groups (85-89% and 91-95%) fall within that range. The study will attempt to keep babies in one of these two smaller ranges.

If you agree to allow your child to be in this study, the following will happen to your child:
Prior to delivery, and after your permission, your baby will be randomized (chosen by chance like the flip of a coin) to one of two lung treatment strategies. The treatments are as follows:
1) CPAP in the delivery room immediately after birth and continuing in the NICU, or
2) The placement of a tube in his/her trachea (windpipe) in the delivery room followed by surfactant administration and ventilation (breathing for the baby using a machine).

In addition to being randomly assigned to one of the two groups described above, your baby will be randomized to a High reading or Low reading oximeter (a monitor that displays how much oxygen is in the blood). The oximeters (oxygen monitors) used in this trial are FDA approved oximeters which have been modified for research purposes. This modification makes the monitors show a value which is either slightly higher or slightly lower than the true oxygen level when values are between 85 and 95%. Outside those ranges, the oximeter works the same as the standard of care device.

Which group your baby is randomized to will not be known to the nurse taking care of your baby, or his/her physician. Only the study coordinator will know which group your baby is in. Within the range of oxygen which we normally keep babies in, your baby will either be on the high end of normal or the low end of normal. He/she will remain on this device until he/she reaches 36 weeks adjusted age. (e. g. 24 wks gestation plus 12 weeks of age = 36 weeks adjusted age). Other care will be conducted as normal during his/her participation in the study. Your baby will be followed in our Infant Follow-up clinic at 6 and 12 months as standard of care for small babies. At 18-22 months corrected age your baby will receive, at no charge to you, a complete exam of their muscles, nerves, and mental and coordinated movement skills. Before discharge from the NICU and at 6, 12 and 18-22 month of age you will be contacted by telephone to discuss your baby's breathing. A respiratory history questionnaire will be administered to help assess the effect of treatment in one of the two groups mentioned above. Your baby's doctor will be contacted to obtain the diagnoses and treatments he or she provided for your baby's breathing.

Participation in this study may involve some added risks or discomforts. Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby. Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted ventilation (methods to help them breathe). If the attending physician deems this necessary, participation in the study will not affect this decision. Some unknown risks may be learned during the study. If these occur, you will be informed by the study personnel. The only other risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential. There will be no name or other patient identification in any study report that may be published after the study is completed. Measures taken to protect you and your baby's identity are described in the confidentiality section of this document.

There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen near discharge) or wheezing in the first 2 years and/or a decrease in the need for eye surgery as a result of exposure to oxygen. Because we do not know in advance the actual strategies chosen for your child, or which of the treatment strategies is the most effective, it is also possible that your baby will receive no direct benefit. The knowledge learned from this study may help us treat babies in the future. However, as noted above, each of the 4 possible combinations of treatments is considered by some units to represent their desired approach.

If your child is injured as a direct result of participation in this research, the University of California will provide any medical care your child needs to treat those injuries. The University will not provide any other form of compensation to you if your child is injured. You may call the UCSD Human Research Protections Program office at (858) 455-5050 for more information

about this, or to inquire about your rights as a research subject, or to report research-related problems.

_____ has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Wade Rich, the Study Coordinator, or Renee Bridge, the Research Nurse, at 619-543-6560. You may contact the principal investigator Dr. Neil Finer at 619-543-3794

As an alternative to participation in this study you may decide to have your baby's doctor decide which treatment your baby will receive. If you decide not to include your child in this study, none of his/her medical information will be included in the study data. Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care your child will receive at this institution of other loss of benefits to which your child is entitled. If you withdraw your child from the study, the attending physician will decide whether to maintain current treatment or change it, based on your child's needs at the time of the decision. Data collection for research purposes will stop at that time.

Clinical information will be collected from your baby's chart by study personnel at UCSD. Information will be labeled with a code number. Coded information will be sent to the NICHD Neonatal Network's Data Collection Center at Research Triangle Institute (RTI) in Research Triangle Park, North Carolina. The study log linking the code number with your baby's identity will be kept under lock and key at UCSD. Information directly identifying your baby will not leave UCSD. Research records will be kept confidential to the extent provided by law.

You may withdraw your child from the study for any reason. In addition, the study doctors may decide to withdraw your child if they feel it is in his/her best interest to do so.

You have received a copy of this consent document to keep and the Experimental Subject's Bill of Rights

You agree to have your child participate.

_____

Parent's or legal guardian's signature DATE

_____

Relationship of legal guardian to subject DATE

_____

Signature of person explaining and getting consent DATE

SUPPORT FOLLOW ON STUDY
RESPIRATORY OUTCOMES

ADMINISTERED AT 18-22 MONTH FOLLOW UP VISIT

This interview should be completed by the parent/guardian for:

_____

All questions pertain only to his/her health.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Respiratory Outcome Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing concerns your child may have.

VOLUME OF OUTPATIENT PULMONARY CARE

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

4a. Has his/her chest ever sounded wheezy or whistling?
   3. Yes
   4. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?

1	2	3	4	5
Very rarely				On Most days

e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing ~

g. Has this child's wheezing/whistling occurred as attacks?
   1. Yes
   2. No

h. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

i. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 21 AND 22

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY (continued)

5a. Has this child ever had a cough when he/she did not have a cold?

1. Yes
2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6a

b. At what time of the day has this cough usually occurred? (CIRCLE ALL THAT APPLY)

1. In the morning, shortly after rising
2. Later in the day
3. During the night
4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?

1. Yes
2. No

d. How often has this child been bothered by coughing?

1 2 3 4 5
Very Rarely — On most days

e. How old was the child when he/she first began to cough?

____ months

f. How old was this child when he/she stopped coughing?

_____ months

OR: check here if child is still coughing: _

g. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?

1. Yes
2. No

h. Has he/she ever seen a doctor about the cough?

1. Yes
2. No

6a. During the past **two weeks**, how often has your child had coughing, wheezing, or shortness of breath *during the day*?

1☐ Never
2☐ Twice a week
3☐ More than two times a week, but not every day
4☐ Everyday, but *not* all the time
5☐ Everyday, all the time

6b. During the past **two weeks**, how often has your child had coughing, wheezing, or shortness of breath *during the night*?

1☐ Never
2☐ Once every two weeks or less
3☐ Once a week
4☐ More than 1 night a week
5☐ Frequently/Every night

6c. Over the past **two weeks (out of 14 days),** how many **days** did you have to change for daytime or evening plans because of your child's asthma: _____# of days

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY (continued)

7a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 8a

IF **YES** TO QUESTION 7A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: ~

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ months

OR: check here if doctor never said he/she had asthma: ~

e. **During the past 6 months**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past 6 months**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 21 AND 22

8a. Has your child ever had bronchiolitis, or any wheezing illness in the first year of life not due to asthma?

1. Yes
2. No . . . SKIP TO QUESTION 9a

IF **YES** TO QUESTION 8A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. How old was this child when he/she had the last such episode?

_____ months

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY (continued)

9a. Has your child ever had bronchitis?
1. Yes
2. No . . . SKIP TO QUESTION 10

IF **YES** TO QUESTION 9a:

b. How old was he/she when the last episode occurred? _____ months
OR: check here if child still has bronchitis ___

c. How often has this child had bronchitis?
1. one episode only
2. 2-3 episodes
3. 4 or more separate episodes
4. almost constantly

d. During the past 6 months, how much trouble did he/she have with bronchitis?
1 2 3 4 5
None A great deal

e. During the past 6 months, did this child take any medicine for bronchitis?
1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES. BE SURE TO COMPLETE QUESTIONS 21 AND 22

10a. Has your child ever had croup?
1. Yes
2. No . . . SKIP TO QUESTION 11

IF **YES** TO QUESTION 10a:

b. Was this diagnosed by a doctor?
1. Yes
2. No

c. Did the child have one or more episodes of croup?
1. One episode
2. More than one episode

11a. Has your child **ever** had pneumonia?
1. Yes
2. No . . . SKIP TO QUESTION 12

IF **YES** TO QUESTION 11a:

b. Was this diagnosed by a doctor?
1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?
1. One episode
2. More than one episode

d. Did your baby receive antibiotics?
1. Yes
2. No

ASCERTAINMENT OF RESPIRATORY EXPOSURES

12a. In the past 6 months, did your baby receive mother's breast milk, either at breast, from a bottle or through a tube?

1. Yes
2. No

IF **YES** TO QUESTION 12a:

12b. For how many months was this child breast-fed or received mostly breast milk?

1. Never breastfed / no breast milk
2. Less than 1 month
3. 1-3 months
4. 4-6 months

13a. Has the **mother** smoked at all since this child was born?

3. Yes
4. No . . . SKIP TO QUESTION 14a

IF **YES** TO QUESTION 13a:

b. For how many months did the mother smoke since this child was born? _____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (Note: One Pack Contains 20 Cigarettes)

_____ cigarettes _____ pipes _____cigars _____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?

_____ Never _____ Occasionally _____Frequently

14. Please choose which of the following options best describe the situation regarding smoking in this child's **home**:

$_1$❑ Smoking is allowed in any common room of the home
$_2$❑ Smoking is limited to part of the house where the child rarely goes
$_3$❑ There is no smoking inside at all → Are there any exceptions to this situation?

$_0$❑ No $_1$❑ Yes

Under what circumstances are the exceptions allowed?

_____

15. Please choose which of the following options best describe the situation regarding smoking in your **car**:

$_1$❑ Do not have a car
$_2$❑ Smoking is usually or always allowed
$_3$❑ Smoking is sometimes allowed
$_4$❑ Smoking occurs in the car only when the child is not inside
$_5$❑ There is no smoking inside the car → Are there any exceptions to this situation?

$_0$❑ No $_1$❑ Yes

Under what circumstances are the exceptions allowed?

_____

16. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

16a. How much does this child's primary caregiver smoke?

$_0$❑ Never $_1$❑ Occasionally $_2$❑ Daily

17. How many children other than this child and his/her siblings live in your house? _____

18. Do you have any pets?

1. Yes
2. No

$_1$❑ Dogs #: _____
$_2$❑ Cats #: _____
$_3$❑ Other #: _____

Appendix C

OUTPATIENT RESPIRATORY CARE

PROPHYLAXIS

19. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?
    1. Yes
    2. No

20. Did this child receive a flu shot?
    1. Yes
    2. No

OXYGEN

21a. Is your child on any oxygen therapy (oxygen tank at home)?
    1. Yes
    2. No

IF **YES** TO QUESTION 21a:

*lpm = liters per minute

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

MEDICATIONS

22. Is your child taking any medicines for asthma or wheezing?
    1. Yes
    2. No
    3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as:* ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other _____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other _____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

ATOPY HISTORY

23. **During the past year**, for how many days has this child been unable to do his/her usual activities because of illnesses such as chest
(not head) colds, bronchitis, asthma or pneumonia?

_____ days

24. How many head colds (common colds) **per year** does this child usually have?

1. Few (0-3 per year)
2. Some (4-5 per year)
3. Frequent (6-9 per year)
4. Constant (more than 9 per year)

25a. Has your child **ever** had hay fever or any other condition that makes his/her nose runny, stuffy, or itchy **apart** from colds?

1. Yes
2. No . . . SKIP TO QUESTION 26

IF **YES** TO QUESTION 25a:

b. How old was your child when you first noticed this condition?

_____ months

c. How old was this child when he/she stopped having this condition?

_____ months

OR: check here if child still has condition ~

d. When this child has the runny or stuffy nose, does he/she also usually:

Cough?	1. Yes 2. No
Wheeze?	1. Yes 2. No
Have shortness of breath?	1. Yes 2. No

26. Has this child **ever** had allergies which cause nose, eye or lung problems?

1. Yes
2. No

27. Has a doctor **ever** told you that this child had sinus trouble?

1. Yes
2. No

28a. Has this child **ever** been allergic to any food?

1. Yes
2. No

b. Has he/she **ever** been allergic to any medicine?

1. Yes
2. No

29a. Has this child **ever** had eczema (allergic skin rash)?

1. Yes
2. No . . . SKIP TO QUESTION 30a

IF **YES** TO QUESTION 29A:

b. Has a doctor told you this child had eczema?

1. Yes
2. No

c. At what age did the eczema begin?

_____ months

d. How old was this child when he/she last had eczema?

_____ months

OR: check here if child still has eczema ~

30a. Was this child breast fed or did he/she receive mostly breast milk?

1. Yes
2. No . . . SKIP TO QUESTION 31

IF **YES** TO QUESTION 30a:

b. For how many months was this child breast fed?

1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

31. At what age was formula introduced?

1. Never
2. less than 1 month
3. 1-3 months
4. 4-6 months
5. more than 6 months

32. At what age was cow's milk (nonformula) started?

1. Never
2. Less than 1 month
3. 1-3 months
4. 4-6 months
5. 7-9 months
6. 9-11 months
7. 12 or more months

33. At what age did he/she begin to receive table foods?

1. less than 1 month
2. 1-3 months
3. 4-6 months
4. 7-9 months
5. more than 9 months

THANK YOU FOR YOUR COOPERATION

SUPPORT FOLLOW-ON STUDY
RESPIRATORY OUTCOMES

ADMINISTERED AT TIME OF ENROLLMENT
PRIOR TO NICU DISCHARGE

This interview should be completed by the parent/guardian for:

_____

All questions pertain only to his/her health.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Respiratory Outcome Study.

Appendix A

QUESTIONNAIRE: ENROLLED CHILD
(Nurse Administered)

Child's Name: _____

Date: ____/_____/_____
Mo. Day Yr.

Child's Sex 1. Male2. Female

Child's Birthdate _____/_____/_____
Mo. Day Yr.

Person being interviewed:

1. Child's Mother
2. Child's Father
3. Both Parents
4. Child's female guardian
5. Child's male guardian
6. Other woman (SPECIFY RELATIONSHIP) _____
7. Other man (SPECIFY RELATIONSHIP) _____

1. At this time, we would like a little information about the environment in which your new child will grow up. First, how many people live with you in your home?

Total household members: _____

2a. After the first few months, will your child be sharing a room with other family members on a regular basis?

1. Yes
2. No

2b. IF YES: How many people will sleep in the same room with him/her? _____

2c. How many living areas are there in your house, excluding closets and bathrooms?_____

3. Do you have any pets inside the home? If yes record number.
   1. Yes
   2. No

   1❑ Dogs #: _____
   2❑ Cats #: _____
   3❑ Other #: _____

4. Does your home or apartment have air conditioning or some kind of cooling?
   1. Air Conditioning
   2. Evaporative Cooling (Desert Southwest)
   3. Both
   4. None
   5. Other _____
   6. Don't Know

5. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).
   1. Steam or hot water (radiator)
   2. Central gas furnace (furnace)
   3. Electric
   4. Wood Stove
   5. Other
   6. Don't know

6. What fuel is used most for cooking in your home?
   1. Electricity
   2. Gas
   3. Fuel Oil
   4. Wood Stove
   5. Other
   6. Don't Know

7a. Is your child being breast fed or receiving mostly breast milk?
   1. Yes
   2. No...SKIP TO QUESTION 8

IF YES.

b. Will this be supplemented with formula? 1. Yes 2. No

c. When do you think the supplement will begin? _____months

d. Do not know when supplements will begin. 1. Yes 2. No

8. Does the mother plan to work outside the home within the next year?
   1. Yes
   2. No
   3. Don't Know

9a. Will your child be cared for by anyone who is not an immediate family member for a major part of the next year?
   1. Yes
   2. No
   3. Maybe

IF YES or MAYBE to 9a:

b. Where will this care be provided?
   1. The parent or guardian's home?
   2. Home of a relative or private sitter?
   3. Day care setting (non-private) ?
   4. Don't Know

c. Will this involve other children, not counting the child's brothers and sisters?
   1. Yes
   2. No
   3. Maybe

10. Finally, which relative is most likely to have your address in case we lose contact with you?

_____ _____
Name Relationship

_____
Address

_____
Telephone

_____
Cell Phone

_____
Email

SUPPORT FOLLOW ON STUDY
FAMILY HISTORY / FAMILY CONTACT QUESTIONNAIRE - ADMINISTERED PRIOR TO NICU DISCHARGE

1. Name:				
2. Relationship to enrolled child:	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact
3. Age (in years):	______	______	______	______
4. Sex:	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female
5. Does this person currently have:	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
a. Bronchitis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
b. Emphysema?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
c. Bronchiectasis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
d. Asthma?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
e. Inhaled Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
f. Food Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
g. Any other chronic respiratory disease? (SPECIFY)	______ ______	______ ______	______ ______	______ ______
6. How often does this person smoke in the house?	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently

SUPPORT FOLLOW ON STUDY OF RESPIRATORY OUTCOMES

ADMINISTERED BY TELEPHONE AT 6 AND 12 MONTHS CORRECTED AGE

This interview should be completed by the parent/guardian for:

_____

All questions pertain only to his/her health.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Respiratory Outcome Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Before we begin this interview it would be helpful if you could gather any medications your child has been prescribed or has been taking and have them in front of you. Can you do that now or is there a better time to call you?

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing problems your child may have.

VOLUME OF OUTPATIENT PULMONARY CARE

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

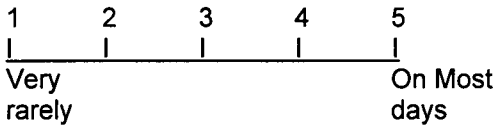
4a. Has his/her chest ever sounded wheezy or whistling?
   3. Yes
   4. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?



e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing ~

g. Has this child's wheezing/whistling occurred as attacks?
   1. Yes
   2. No

h. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

i. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 21 AND 22

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY (continued)

5a. Has this child ever had a cough when he/she did not have a cold?

1. Yes
2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6a

b. At what time of the day has this cough usually occurred? (CIRCLE ALL THAT APPLY)

1. In the morning, shortly after rising
2. Later in the day
3. During the night
4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?

1. Yes
2. No

d. How often has this child been bothered by coughing?

1 2 3 4 5

Very Rarely — On most days

e. How old was the child when he/she first began to cough?

____ months

f. How old was this child when he/she stopped coughing?

_____ months

OR: check here if child is still coughing: _

g. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?

1. Yes
2. No

h. Has he/she ever seen a doctor about the cough?

1. Yes
2. No

6a. During the past **two weeks**, how often has your child had coughing, wheezing, or shortness of breath *during the day*?

1❑ Never
2❑ Twice a week
3❑ More than two times a week, but not every day
4❑ Everyday, but *not* all the time
5❑ Everyday, all the time

6b. During the past **two weeks**, how often has your child had coughing, wheezing, or shortness of breath *during the night*?

1❑ Never
2❑ Once every two weeks or less
3❑ Once a week
4❑ More than 1 night a week
5❑ Frequently/Every night

6c. Over the past **two weeks (out of 14 days),** how many **days** did you have to change for daytime or evening plans because of your child's asthma: _____# of days

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY (continued)

7a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 8a

IF **YES** TO QUESTION 7A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: ~

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ months

OR: check here if doctor never said he/she had asthma: ~

e. **During the past 6 months**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past 6 months**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 21 AND 22

8a. Has your child ever had bronchiolitis, or any wheezing illness in the first year of life not due to asthma?

1. Yes
2. No . . . SKIP TO QUESTION 9a

IF **YES** TO QUESTION 8A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. How old was this child when he/she had the last such episode?

_____ months

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY (continued)

9a. Has your child ever had bronchitis?

1. Yes
2. No . . . SKIP TO QUESTION 10

IF **YES** TO QUESTION 9a:

b. How old was he/she when the last episode occurred? _____ months
OR: check here if child still has bronchitis ___

c. How often has this child had bronchitis?

1. one episode only
2. 2-3 episodes
3. 4 or more separate episodes
4. almost constantly

d. During the past 6 months, how much trouble did he/she have with bronchitis?

1 2 3 4 5
| | | | |
None A great deal

e. During the past 6 months, did this child take any medicine for bronchitis?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES. BE SURE TO COMPLETE QUESTIONS 21 AND 22

10a. Has your child ever had croup?

1. Yes
2. No . . . SKIP TO QUESTION 11

IF **YES** TO QUESTION 10a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of croup?

1. One episode
2. More than one episode

11a. Has your child **ever** had pneumonia?

1. Yes
2. No . . . SKIP TO QUESTION 12

IF **YES** TO QUESTION 11a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?

1. One episode
2. More than one episode

d. Did your baby receive antibiotics?

1. Yes
2. No

ASCERTAINMENT OF RESPIRATORY EXPOSURES

12a. In the past 6 months, did your baby receive mother's breast milk, either at breast, from a bottle or through a tube?

1. Yes
2. No

IF **YES** TO QUESTION 12a:

12b. For how many months was this child breast-fed or received mostly breast milk?

1. Never breastfed / no breast milk
2. Less than 1 month
3. 1-3 months
4. 4-6 months

13a. Has the **mother** smoked at all since this child was born?

3. Yes
4. No . . . SKIP TO QUESTION 14a

IF **YES** TO QUESTION 13a:

b. For how many months did the mother smoke since this child was born? _____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (Note: One Pack Contains 20 Cigarettes)

_____ cigarettes _____ pipes _____cigars _____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?

_____ Never _____ Occasionally _____Frequently

14. Please choose which of the following options best describe the situation regarding smoking in this child's **home**:

$_1$❑ Smoking is allowed in any common room of the home
$_2$❑ Smoking is limited to part of the house where the child rarely goes
$_3$❑ There is no smoking inside at all → Are there any exceptions to this situation?

$_0$❑ No $_1$❑ Yes

Under what circumstances are the exceptions allowed?

_____

15. Please choose which of the following options best describe the situation regarding smoking in your **car**:

$_1$❑ Do not have a car
$_2$❑ Smoking is usually or always allowed
$_3$❑ Smoking is sometimes allowed
$_4$❑ Smoking occurs in the car only when the child is not inside
$_5$❑ There is no smoking inside the car → Are there any exceptions to this situation?

$_0$❑ No $_1$❑ Yes

Under what circumstances are the exceptions allowed?

_____

16. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

16a. How much does this child's primary caregiver smoke?

$_0$❑ Never $_1$❑ Occasionally $_2$❑ Daily

17. How many children other than this child and his/her siblings live in your house? _____

18. Do you have any pets inside the home? If yes record number.

1. Yes
2. No

$_1$❑ Dogs #: _____
$_2$❑ Cats #: _____
$_3$❑ Other #: _____

Appendix B

OUTPATIENT RESPIRATORY CARE

PROPHYLAXIS

19. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?
    1. Yes
    2. No

20. Did this child receive a flu shot?
    1. Yes
    2. No

OXYGEN

21a. Is your child on any oxygen therapy (oxygen tank at home)?
    1. Yes
    2. No

IF **YES** TO QUESTION 21a:

*lpm = liters per minute

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

MEDICATIONS

22. Is your child taking any medicines for asthma or wheezing?
    1. Yes
    2. No
    3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as*: ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

THANK YOU FOR YOUR COOPERATION

SUPPORT Trial Pulmonary Outcomes Follow On Study

Response to Follow Up PI *"Additional"* Comments

Timothy P. Stevens, MD, MPH

7/12/05

REVIEWER 1 (Ron Heyne)

Comment 1: .....just ran across two interesting articles from the UK assessing accuracy of parents' interpretations of children's respiratory symptoms: Cane and McKenzie "Parents interpretations of children's respiratory symptoms on video" Arch Dis Child2001; 84:31-34 and Elphick et. al. "Survey of respiratory sounds in infants" Arch Dis Child 2001; 84:35-39.

Response to comment 1: *These articles reinforce a point made by the reviewer in previous comments, i.e. there can variation in the words and descriptions used to characterize wheezing. The variability can result from both language and colloquial differences. This is a very important issue. To address this issue more fully, the protocol has been modified as follows:*

*"**G.4.1.1 Standard Definition of Wheezing***

Several studies have found that multiple colloquialisms in both English and Spanish can be used to describe wheezing (1-5), creating opportunity for misinterpretation of respiratory sounds and potential for over or under estimation of the incidence of wheezing. Other studies have found that clips of respiratory sounds played for families improve accuracy of symptom reporting (6;7), providing data relatively free from biases due to language, culture, literacy or interviewing techniques. To minimize variation in interpretation of respiratory sounds as wheezing we will provide a verbal AND a brief audio clip that can be played for the interviewee at the beginning of the interview (electronic Appendix D). Accompanying the audio clip, wheezing will be defined verbally by the interviewer as an expiratory sound (a sound that is made when breathing out, not in) coming from the chest, sometimes described as whistling or musical. Although not yet widely used, use of audio clips to standard symptom definition is the best approach to bridge the language gap that exists between English and Spanish and among Spanish speaking populations using different dialects or colloquialisms.

In administering the questionnaires, every effort will be made to accurately measure the occurrence of pulmonary symptoms and health care and medication use, thus establishing the true incidence of pulmonary morbidity in the study population as a whole. Most importantly, however, because pulmonary morbidity is a blinded outcome measure from a randomized controlled trial, bias favoring one study arm over another should not occur."

Comment 2: .....We need to provide some incentive for participation, since this will involve additional time and trouble on the part of the family;

Response to comment 2: *Funds to compensate families were not requested in the original budget proposal. If follow up PIs feel strongly on this point, additional funds to support incentives can be sought from NICHD to compensate families.*

Comment 3: .....as in the case of the PCV7 study, we need the flexibility to be able to enroll and obtain the baseline questionnaire within 2-4 weeks after discharge (at our first follow-up visit), rather than prior to discharge, which is a more challenging time to try to connect with our families).

Response to comment 3: *Establishing the first contact at 2-4 weeks rather than prior to hospital discharge should not create a problem.*

REVIEWER 2 (Janet Morgan)

Comment 1: .....I had a few questions regarding the interviews done at 6,12, 18 months and discharge. On the 6,12 and 18 month interviews the question #18 asked about pets but does not specify indoors or out, the discharge interview separates indoor from outdoors pets. Do we assume that after discharge that question is not as important?

Response to comment 1: *Thank you for pointing this out. For infants in the first 2 years of age, indoor pets are most relevant in assessing dander exposures. In the revised questionnaires, this is now clear.*

Comment 2: .....I am unsure of who I would ask the questions on the last page of the appendix. The questions ask for name, relationship, age, sex and several other questions, but I did not understand who to ask these question.

Response to comment 2: *These questions are posed to the guardian at the time of discharge. The guardian provides both family history (parents, grandparents and siblings) and provides environmental tobacco smoke exposure for current household contacts.*

Reference List

(1) Cane R, Pao C, McKenzie S. Understanding childhood asthma in focus groups: perspectives from mothers of different ethnic backgrounds. BMC Fam Pract. 2001;2:4.

(2) Cane RS, McKenzie SA. Parents' interpretations of children's respiratory symptoms on video. Arch Dis Child. 2001;84:31-34.

(3) Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? Arch Dis Child. 2000;82:327-32.

(4) Davies MJ, Cane R, Ranganathan S, McKenzie SA. Cough, wheeze and sleep. Arch Dis Child. 1998;79:465.

(5) Elphick HE, Sherlock P, Foxall G, Simpson EJ, Shiell NA, Primhak RA et al. Survey of respiratory sounds in infants. Arch Dis Child. 2001;84:35-39.

(6) Beasley R, Lai CK, Crane J, Pearce N. The video questionnaire: one approach to the identification of the asthmatic phenotype. Clin Exp Allergy. 1998;28 Suppl 1:8-12.

(7) Shaw RA, Crane J, Pearce N, Burgess CD, Bremner P, Woodman K et al. Comparison of a video questionnaire with the IUATLD written questionnaire for measuring asthma prevalence. Clin Exp Allergy. 1992;22:561-68.

From: Neil Finer
To: "Kathy J Auten"; npeters@wfubmc.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: oximeter to Duke
Date: Thursday, July 14, 2005 2:32:52 PM

Thanks Nancy and Kathy.
You guys are awesome.
Neil

From: Kathy J Auten [mailto:auten002@mc.duke.edu]
Sent: Thursday, July 14, 2005 9:24 AM
To: Neil Finer; Wade Rich
Subject: Fw: oximeter to Duke

FYI.
----- Forwarded by Kathy J Auten/Pediatrics/mc/Duke on 07/14/2005 12:23 PM -----
Kathy J Auten

07/14/2005 11:39 AM

To: "Nancy Peters" <npeters@wfubmc.edu>
cc: "Hastings, Betty J." <bkh@rti.org>, "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
Subject: Re: oximeter to Duke Link

We received it. Many thanks!

"Nancy Peters"
<npeters@wfubmc.edu>

07/13/2005 12:56 PM

To: "Hastings, Betty J." <bkh@rti.org>, "Kathy J Auten" <auten002@mc.duke.edu>
cc: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
Subject: oximeter to Duke

Betty,

I am shipping docking station SN 059166 and oximeter SN 311139 (orange) to Center 19, Duke University Medical Center, by overnight Fed Ex.

Nancy P

From: Gaynelle Hensley
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT OXimeters
Date: Tuesday, June 14, 2005 1:57:42 PM

Rosemary, I am shipping two monitors to Wade. Should arrive tomorrow.
Gay

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 06/14/05 9:18 AM >>>
Hi Gay

I spoke with Charles this am and he thought that your site could spare a few oximeters for the UCSD site (they have consents from twins and triplets and not enough oximeters if the moms deliver).

Wade will send you a FED EX delivery address and let you know how many to send.

Thanks much!!
Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; "Nancy Peters"; "Michael O`Shea"
Cc: "Kathy J Auten"; goldb008@mc.duke.edu; "Hastings, Betty J."
Subject: RE: oximeters
Date: Thursday, July 14, 2005 10:09:46 AM

Thanks Nancy
Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, July 13, 2005 10:00 AM
To: Nancy Peters; Michael O`Shea
Cc: Kathy J Auten; goldb008@mc.duke.edu; Hastings, Betty J.; nfiner@ucsd.edu
Subject: RE: oximeters

Nancy
Thanks for being so quick!!!
Rose

From: Nancy Peters [mailto:npeters@wfubmc.edu]
Sent: Wednesday, July 13, 2005 11:54 AM
To: Higgins, Rosemary (NIH/NICHD); Michael O`Shea
Cc: Kathy J Auten; goldb008@mc.duke.edu; Hastings, Betty J.
Subject: RE: oximeters

Yes, I can send them one. If they need it today then I can drive and meet Kathy half way between Duke and WF and give it to her. Kathy, why don't you give me a call and let me know how you want it sent to you.

Nancy

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, July 13, 2005 11:28 AM
To: Michael O`Shea; Nancy Peters
Cc: Kathy J Auten; goldb008@mc.duke.edu; Hastings, Betty J.
Subject: oximeters

Hi Mike and Nancy
Is there any possibility that you could spare one ORANGE oximeter for the Duke Site? – they have (b) (6) and only have two orange oximeters available. Let me know
Thanks in advance!
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
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MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909

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

From: Nancy Peters
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: oximeters
Date: Wednesday, July 13, 2005 1:08:57 PM

I was happy to be able to help. If we are not actively enrolling then at least I can help others. I am certainly overjoyed that my staff has completed their back to back and somewhat overlapping vacations-- -- so that I can get back to trying to do my job and hopefully remove the black smudge beside the WF tardy list.

Nancy

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, July 13, 2005 1:00 PM
To: Nancy Peters; Michael O`Shea
Cc: Kathy J Auten; goldb008@mc.duke.edu; Hastings, Betty J.; nfiner@ucsd.edu
Subject: RE: oximeters

Nancy
Thanks for being so quick!!!
Rose

From: Nancy Peters [mailto:npeters@wfubmc.edu]
Sent: Wednesday, July 13, 2005 11:54 AM
To: Higgins, Rosemary (NIH/NICHD); Michael O`Shea
Cc: Kathy J Auten; goldb008@mc.duke.edu; Hastings, Betty J.
Subject: RE: oximeters

Yes, I can send them one. If they need it today then I can drive and meet Kathy half way between Duke and WF and give it to her. Kathy, why don't you give me a call and let me know how you want it sent to you.

Nancy

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, July 13, 2005 11:28 AM
To: Michael O`Shea; Nancy Peters
Cc: Kathy J Auten; goldb008@mc.duke.edu; Hastings, Betty J.
Subject: oximeters

Hi Mike and Nancy
Is there any possibility that you could spare one ORANGE oximeter for the Duke Site? – they have (b) (6) and only have two orange oximeters available. Let me know
Thanks in advance!
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Petrie, Carolyn
To: Das, Abhik; Poole, W. Kenneth; Gantz, Marie; Schaefer, Scott E.; wrich@ucsd.edu; Neil Finer
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn
Subject: SUPPORT Oximetry call Wed Jul 27, 1-2pm ET
Date: Tuesday, July 12, 2005 2:38:19 PM

The SUPPORT Oximetry call to discuss the function of oximeters and downloads is scheduled for

Wednesday, July 27
1:00-2:00 pm ET (10:00-11:00 am PT)

To join the call:
Dial Tollfree: **866-675**(b) (6)
Passcode: (b) (6) (# when prompted)

Leader: Rose Higgins

From: Das, Abhik
To: nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Petrie, Carolyn
Subject: RE: SUPPORT Oximeter Downloads
Date: Monday, July 11, 2005 1:59:42 PM

Neil:

I have already asked Carolyn to set up a call so that we can discuss these issues and get a fix on what exactly the questions are, and take it from there. Besides myself and Ken, we are planning on having Scott and Marie from RTI on this call as well. I hope you and Wade can attend from your end. (Rose is welcome as well if she wants to.)

Thanks

Abhik

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, July 11, 2005 1:49 PM
To: Das, Abhik
Cc: 'Higgins, Rosemary (NIH/NICHD)'; Poole, W. Kenneth
Subject: SUPPORT Oximeter Downloads

Hi Abhik
I want to determine if we have a problem with SUPPORT oximetry data downloads. I know that Wade has discussed this with Scott, but I do not believe that we have a satisfactory answer to the present time. The major issue was the apparent gaps in the data, some of which, I understand, was related to the oximeter being taken off the infant and then reapplied.
However, we need clarity regarding the other gaps, if there are any. I would appreciate your assistance in getting to the bottom of this issue.

Many Thanks
Neil Finer

From: Higgins, Rosemary (NIH/NICHD)
To: Poole, W. Kenneth
Subject: RE: SUPPORT Enrollment
Date: Friday, July 08, 2005 1:59:00 PM

Can I tell them???
Thanks
Rose

From: Poole, W. Kenneth [mailto:poo@rti.org]
Sent: Friday, July 08, 2005 1:59 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT Enrollment

Looks like 72 in the data base.

> -----Original Message-----
> **From:** Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> **Sent:** Friday, July 08, 2005 1:53 PM
> **To:** Poole, W. Kenneth
> **Subject:** RE: SUPPORT Enrollment
>
> OK THANKS
> ROSE

> **From:** Poole, W. Kenneth [mailto:poo@rti.org]
> **Sent:** Friday, July 08, 2005 1:52 PM
> **To:** Higgins, Rosemary (NIH/NICHD)
> **Subject:** RE: SUPPORT Enrollment
>
> Don't think so.
>
> > -----Original Message-----
> > **From:** Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> > **Sent:** Friday, July 08, 2005 12:59 PM
> > **To:** Poole, W. Kenneth
> > **Subject:** SUPPORT Enrollment
> >
> > Ken
> > Any chance you could tell us how many kids are enrolled in SUPPORT for the call?
> > Thanks
> > Rose
> >
> > Rosemary D. Higgins, M.D.
> > Program Scientist for the Neonatal Research Network
> > Pregnancy and Perinatology Branch
> > Center for Developmental Biology and Perinatal Medicine
> > NICHD, NIH
> > 6100 Executive Blvd., Room 4B03B
> > MSC 7510
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> > (For overnight delivery, use Rockville, MD 20852)
> > 301-435-7909
> > 301-496-3790 (FAX)
> > higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD)
To: Wally Carlo, M.D.; Petrie, Carolyn
Subject: RE: SUPPORT conf call Fri Jul 8, 1pm ET
Date: Thursday, July 07, 2005 1:07:00 PM

Yes, I also have a note to discuss authorship.
Thanks
Rose

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, July 07, 2005 1:06 PM
To: Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT conf call Fri Jul 8, 1pm ET

Rose and Carolyn: Could we add the saturation compliance monitoring to the call? I circulated the ideas to consider a few days ago. wally

---

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Thursday, July 07, 2005 12:00 PM
To: Petrie, Carolyn; Das, Abhik; Poole, W. Kenneth; Duara, Shahnaz; Edward Donovan; Wally Carlo, M.D.; mcw3@po.cwru.edu; Higgins, Rosemary (NIH/NICHD); wrich@ucsd.edu; reverett@med.miami.edu; Hastings, Betty J.; Zaterka-Baxter, Kristin; Barbara Stoll
Cc: Neil Finer; [SCRN] Dunbar-Scott, Renee; [SCRN] Tinsley, Mazie; fmartinez@ucsd.edu
Subject: RE: SUPPORT conf call Fri Jul 8, 1pm ET

Reminder for tomorrow's call:

The SUPPORT conference call is scheduled for
Friday July 8
1:00-2:00pm ET (10-11am PT)

Agenda

- How to fill out screening logs (eligible versus screening)
- Definition of BPD at 36 weeks – three different definitions currently (Dr. Stoll for GDB)
- Pulmonary outcomes secondary

To join the call:
Dial Tollfree: **866-675-**(b) (6)
Passcode: [redacted](b)(# when prompted)

Leader: Rose Higgins

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 902
Rockville, MD 20852

ph. (301) 230-4648
fx. (301) 230-4646

From: Wally Carlo, M.D.
To: Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT conf call Fri Jul 8, 1pm ET
Date: Thursday, July 07, 2005 1:06:08 PM

Rose and Carolyn: Could we add the saturation compliance monitoring to the call? I circulated the ideas to consider a few days ago. wally

---

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Thursday, July 07, 2005 12:00 PM
To: Petrie, Carolyn; Das, Abhik; Poole, W. Kenneth; Duara, Shahnaz; Edward Donovan; Wally Carlo, M.D.; mcw3@po.cwru.edu; Higgins, Rosemary (NIH/NICHD); wrich@ucsd.edu; reverett@med.miami.edu; Hastings, Betty J.; Zaterka-Baxter, Kristin; Barbara Stoll
Cc: Neil Finer; [SCRN] Dunbar-Scott, Renee; [SCRN] Tinsley, Mazie; fmartinez@ucsd.edu
Subject: RE: SUPPORT conf call Fri Jul 8, 1pm ET

Reminder for tomorrow's call:

The SUPPORT conference call is scheduled for
Friday July 8
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- How to fill out screening logs (eligible versus screening)
- Definition of BPD at 36 weeks – three different definitions currently (Dr. Stoll for GDB)
- Pulmonary outcomes secondary

To join the call:
Dial Tollfree: **866-675**(b) (6)
Passcode: [redacted](b)(# when prompted)

Leader: Rose Higgins

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 902
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: William Oh
To: Abbot Laptook; WCarlo@peds.uab.edu; goldb008@mc.duke.edu; mazie_tinsley@oz.ped.emory.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: secondary to support trial
Date: Thursday, July 07, 2005 12:02:32 PM

Abbot: I appreciate your candid assessment. I would like to know how the others feel and I will of course abide by the group's decision.

Bill

From: Abbot Laptook
Sent: Thursday, July 07, 2005 9:50 AM
To: William Oh; WCarlo@peds.uab.edu; goldb008@mc.duke.edu; Mazie Tinsley [mazie_tinsley@oz.ped.emory.edu]
Cc: higginsr@mail.nih.gov
Subject: RE: secondary to support trial

Bill

I have reviewed the proposal and these are my honest opinions. I would be surprised if the Network is enthusiastic to take on this secondary for two reasons: First it is purely observational with regard to whether infants with different rates of death/BPD have different extents of weight loss and fluid/Na intakes. This in essence would repeat observations previously done by the Network using data of the GDB and the glutamine trial. Without a specific intervention to alter fluid/Na management and its impact on death/BPD, I don't think we will be further along in understanding the role of ECF contraction and this outcome. The second reason is that this is quite an intensive data collection for the first week of life when you consider all data items, some of which may be hard to find (eg flush for medications). The Support trial at present is very labor intensive at the outset when you consider that we are averaging 4 consented moms for each enrolled infant and we have to approach 2 moms for everyone that is consented. Bottom line, I don't see this flying. AL

From: William Oh
Sent: Tuesday, July 05, 2005 7:42 AM
To: WCarlo@peds.uab.edu; goldb008@mc.duke.edu; Mazie Tinsley [mazie_tinsley@oz.ped.emory.edu]; Abbot Laptook
Cc: higginsr@mail.nih.gov
Subject: secondary to support trial

Good morning everyone: You may recall that during the Steering Committee meeting I indicated that it might be important to take the opportunity of collecting weight loss, fluid and sodium intakes data on infants randomized in SUPPORT trial

to confirm the hypothesis that we tried so hard in the writing of the sodium and fluid restriction protocol. I put together a proposal for submission to the SUPPORT subcomittee for consdieration. Since you folks were so instrumental in putting the fluid restriction protocol together, I would like to include you as the work group in putting this protocol together. I would appreciate your taking a little time out of your busy schedule to give me your inputs.

Thanks

Bill

From: Edward Donovan
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: Pulmonary outcomes secondary study
Date: Wednesday, July 06, 2005 11:55:40 AM

---

rochester.
I don't think we got a good answer on "validation" from Tim?

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu
>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 07/05/05 12:14 PM >>>
Hi,

I need to know if your site will perform this study or if you wish to have
the Rochester site perform the questionnaires for your site.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD)
Sent: Friday, June 17, 2005 10:07 AM
To: Abbot Laptook (alaptook@WIHRI.org); 'Abhik Das'; 'Brenda Poindexter';
'Carlo Waldemar (E-mail)'; 'Charles Rosenfeld'; 'Dale Phelps'; 'Ed Donovan';
'Ehrenkranz Richard (E-mail)'; 'Jobe Alan (E-mail)'; 'Lemons Jim (E-mail)';
'Michael O'Shea'; 'Michelle Walsh'; 'Neil Finer'; 'Oh William (E-mail)';
'Poole Kenneth (E-mail)'; 'Ronald GOldberg'; 'Shahnaz Duara'; 'Shankaran Seetha (E-mail)'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)';
'Tyson Jon (E-mail)'; Walid Salhab (Walid Salhab); Anna Dusick (adusick@iupui.edu); Betty Vohr ('Betty_Vohr@brown.edu'); Charlie Bauer (cbauer@peds.med.miami.edu); Dee WIlson (b) (6) Gary Myers (Gary_myers@URMC.Rochester.edu); 'Ira Adams-Chapman'; Jean Steichen (steichjj@email.uc.edu); Myriam Peralta (mperalta@peds.uab.edu); Ricki Goldstein (golds005@mc.duke.edu); 'Robert Dillard'; 'Roy Heyne'; 'Susan Hintz'; Yvette Johnson (yjohnson@med.wayne.edu); Yvonne Vaucher (Yvonne Vaucher)
Cc: 'Hastings, Betty J.'; (kzaterka@rti.org); 'Petrie, Carolyn'
Subject: Pulmonary outcomes secondary study

Hi

Attached are documents and questionnaires associated with the pulmonary outcomes secondary study to the SUPPORT Trial. Please review the documents
and send me a preference by June 27 indicating the following:
1. My site will do the Questionnaires

2. Rochester site to do questionnaires on my study subjects

I am checking on the issues regarding how the consents would be phrased in
order that information could pass from your site to the Rochester site.

Thanks in advance for all your help!!
Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

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301-496-3790 (FAX)

higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

From: Neil Finer
To: "Barbara Stoll"
Cc: "wade rich"; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Tuesday, July 05, 2005 7:49:49 PM

Hi Barbara
Congratulations
Absolutely - If the baby is on room air defeat the high alarm.
Hopefully the pH will get better - Its amazing how these babies act.
Thanks for your center's great enrollment
Neil
-----Original Message-----
From: Barbara Stoll [mailto:barbara.stoll@oz.ped.emory.edu]
Sent: Tuesday, July 05, 2005 11:03 AM
To: nfiner@ucsd.edu
Cc: higginsr@mail.nih.gov; Susie Buchter
Subject: SUPPORT

Dear Neil

Question-- we are still on the learning curve.....

We have baby # 6.....CONGRATULATIONS to Susie Buchter.....

Baby born (b) (6) 1100 g-- randomized to intub and surfactant. He has been on RA ventilated since adminssion. He has not met the criteria of pH greater than 7.3 to be extubated.

QUESTION: The sat limit is 84-96% and the sat alarm goes off all the time. Can we increase the limit in a baby on room air?

Thanks

BJS

From:	Richard Ehrenkranz
To:	adas@rti.org; dale_phelps@urmc.rochester.edu; Jon.E.Tyson@uth.tmc.edu; moshea@wfubmc.edu; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; sshankar@med.wayne.edu
Cc:	petrie@rti.org; poo@rti.org
Subject:	SUPPORT secondary study
Date:	Wednesday, July 06, 2005 4:05:33 PM
Attachments:	Duara SUPPORT growth prtcl 30Jun05.doc

Hi:
I have attached a postnatal growth study submitted by Shahnaz and Cristina Navarrete as a SUPPORT secondary study. They have submitted 3 options-option #! is the lowest cost, but has the most limitations, while options #2 and #3 will cost more than $10000, but collect more data for analysis. Let's also review this proposal during our conference call on August 4th. Neil, will you comment on it for the SUPPORT subcommittee? Abhik, will prepare comments about the various trade-offs associated with each option? I will also prepare comments as another primary reviewer. Thanks.

The revised probiotics protocol, which will also be discussed on Aug 4th, will be distributed once it is received.
Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study: A Proposed Secondary Study

Cristina Navarrete MD, and Shahnaz Duara MD
University of Miami Miller School of Medicine, Miami, FL.

Abstract:

Post-natal growth restriction is a major problem in preterm infants. Perturbations in oxygenation are recognized to influence post-natal growth; hypoxic conditions can directly impair growth and hyperoxic conditions predispose infants to BPD, which in turn has been linked to poor growth. The NICHD Neonatal Network is conducting a prospective trial of preterm infants randomized to two levels of baseline oxygen saturations. The effect of baseline saturations on pulmonary morbidity and ROP are the primary outcome measures. With respect to post-natal growth, there is a paucity of data relating alterations in baseline oxygen saturation and/or frequent deviations above or below the baseline to growth outcomes. We propose a secondary study to quantify short-term growth velocity in-hospital and long-term growth at 18-22 months of corrected age for infants enrolled in the SUPPORT Trial in relationship to oxygen saturation.

A. Hypothesis to be tested

Primary:

1. Infants in the low oxygen saturation group (85-89%) will have better in-hospital and better long-term (18-22 months corrected age) growth. If growth data are available at multiple time points in the in-hospital period, then we hypothesize that trajectories of growth in hospital will be better for infants in the low oxygen saturation group.

Secondary:

1. Growth will be greater in infants who spend > 50% of the time with daily median oxygen saturation between 85% -95% while on supplemental oxygen, independent of randomization to low or high oxygen saturation.

2. Infants with BPD will have poorer in-hospital and long-term growth than infants without BPD, independent of randomization to low or high oxygen saturation.

3. Long-term growth will be positively related to neuro-developmental outcome, independent of randomization to low or high oxygen saturation.

B. Specific Aims:

1. To determine anthropometric measurements (wt, HC, length) in infants randomized to low and high oxygen saturation arms, from birth to hospital discharge and again at 18-22 months corrected age.
2. To determine nutritional intake (parenteral and enteral) during hospital stay.
3. To determine the percentage of infants with growth <10 percentile at 36 weeks PMA or discharge, whichever comes first.

4. To determine the percentage of infants with growth <10 percentile at 18-22 months corrected age.
5. To determine growth in relation to the proportion of time spent with oxygen saturation
    a. <85% and >95%
    b. 85-95%
6. To determine growth in relation to the proportion of infants with
    a. median oxygen saturation > 95%
    b. median oxygen saturation 75% - 84%
    c. median oxygen saturation < 75%
7. To relate incidence of BPD in low and high saturation arms to growth.
8. To determine in-hospital growth velocity/trajectory in low and high saturation arms.
9. To determine long-term growth velocity/trajectory, from hospital discharge to follow up at 18-22 months corrected age in low and high saturation arms.
10. To relate neuro-developmental outcome at 18-22 months corrected age to long-term growth in low and high saturation arms.

Rationale:

The SUPPORT Trial will randomize infants to two ranges of SpO2 in order to test the hypothesis that use of a lower SpO2 range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity and/or the need for surgical intervention. Retrospective cohort data from several units in the U.K., with different oxygen supplementation policies, revealed poorer growth patterns in the preterm infants exposed to higher oxygen saturations for the duration of oxygen exposure (Tin 2001). Conversely, observational data of infants with established BPD show better growth with home oxygen support (Groothius 1987), and two recent RCT of different target saturations in older oxygen-dependent premature infants showed no difference in short or long-term growth outcomes (STOP-ROP 2000, BOOST Trial 2003). There are no RCT data evaluating the short or long-term growth impact of different SpO2 strategies with supplemental oxygen use in a birth cohort of extremely preterm infants. Therefore, this study provides an opportunity for us to obtain critically needed growth information on premature infants who are exposed from birth to different target oxygen saturation strategies.

Background

Improvements in antenatal care, respiratory support and nutrition have contributed to increased survival of ELBW infants. As the number of survivors increase, the long term outcome of these infants becomes more important. Lemons et al described growth failure or weight <10th percentile at 36 weeks postmenstrual age in 97% of ELBW infants surviving to discharge. Some morbidities in adulthood are linked to growth during the early post-natal period (Singhal 2004) and make adequacy of growth in this population of heightened interest.

Instead of following intra-uterine growth curves of age matched fetuses, VLBW infants exhibit wide-spread post-natal growth retardation (Cooke 2004), losing ground during the first weeks of life (Berry 1997). To resume growth post-natally, nutrition is of paramount importance; however, other factors such as severity of illness and perhaps oxygenation

also play a role. Observational studies of infants with BPD showed poor post-natal growth when infants were sent home without oxygen supplementation (Markestad 1981).

Although preterm infants without lung disease attain oxygen saturations >95%, artificial attempts to keep arterial oxygenation at a "physiological" level may not be beneficial to growth, the lung or retina (Tin 2001). Animal studies have shown that newborn mammals (mice, rats, guinea pigs) develop poor growth with chronic hypoxia and that blunted body growth is directly proportional to the profundity of the exposure to chronic hypoxia (Mortola 1990). Chronic hypoxemia has also been suggested as the cause of poor growth in patients with cyanotic congenital heart disease (Dundar 2000). When home oxygen supplementation was discontinued inappropriately by parents in a cohort of VLBW infants with BPD, there was a deceleration in the rate of weight gain, which improved when oxygen supplementation was resumed (Groothius 1987). Hudak et al in 1989 observed that ELBW infants with CLD who went home on oxygen supplementation had good catch-up growth at 19 months. Taken collectively, these data suggest that hypoxic conditions affect growth negatively and supplementing oxygen may improve growth.

The optimal level of oxygen saturation to promote post-natal growth is unknown. Most of the available human data is limited to oxygen supplementation of infants who are oxygen dependent or have BPD. Baraldi et al demonstrated that discharged infants with BPD, who were kept on supplemental oxygen to keep saturations above 94%, had progressive but poor weight gain (stayed below 3rd percentile) at 9 months corrected age follow-up. In infants with BPD whose oxygen supplementation was intentionally discontinued, the subset who exhibited episodes of desaturations below 88-91% had a significant decline in the rate of weight gain as compared to those who maintained saturations above 92% (Moyer-Mileur 1996). Conversely, when two different oxygen saturation control policies (high: 88-98% and low: 70-90%) were retrospectively reviewed in <28 week gestation infants, the infants being cared for in the high oxygen saturation policy units were more likely to weigh less than the 3rd percentile at discharge (45% vs. 17%, Tin 2001). The infants assigned to the high oxygen saturation limits were also more likely to have BPD and ROP.

Recently, the BOOST Trial demonstrated that randomizing infants born <30 weeks gestation who were still on oxygen at 32 weeks postmenstrual age either to standard saturations (91-94%) or to high saturations (95-98%) produced no significant difference in growth at 12 months corrected age. This study, while randomizing infants to two different levels of saturations (conventional and high), only enrolled infants if they were still on oxygen supplementation at 32 weeks PMA and used higher limits than planned by SUPPORT. Our proposal is novel in that randomization to the two oxygen strategies begins at birth and continues for as long as the infants are in supplemental oxygen - by implementing this secondary we will be able to determine the impact of these strategies on short and long-term growth.

Methods:

OPTION 1: (basic GDB*data – current GDB)
Anthropometric Measures – at birth, 28 days, 36 weeks or discharge (wt, length, HC)
Clinical Data-

1. Date when infant regains birth weight
2. Date of first enteral feed
3. Date of full enteral feeds (enteral > 120ml/kg/d)
4. Total number of days on parenteral nutrition

5. Presence of BPD

OPTION 2: ('snapshots')
OPTION 1 plus additional anthropometric measures – weight, at postnatal days 7, 14, 21, and 32w PMA
Clinical Data – 24 h intake 'snapshots' (Parenteral, Enteral) – postnatal days 7, 14, 21, and 28, 32w PMA, 36w PMA or discharge (whichever comes first)

OPTION 3: (mimic glutamine dataset)
OPTION 1 plus:
Anthropometric Measures by study nurse (wt, length, HC) – weekly, until status
Clinical Data – 24 h intake (Parenteral, Enteral) – daily, until status

Intervention Data – (same for all OPTIONS)

1. Duration of time spent in target saturation ranges of interest (already part of SUPPORT‡)
2. Median values for unmasked oxygen saturation while still on supplemental oxygen therapy
3. Highest daily FiO2‡
4. Duration of supplemental oxygen exposure
5. Documentation of post-discharge oxygen use

Follow Up data – (same for all OPTIONS)

1. Anthropometric measurements at 18-22months corrected age
2. Neuro-developmental follow up at 18-22 months corrected age

Primary Outcome:

Growth in-hospital and at 18-22 months corrected age in high and low saturation arms.

Sample Size:

Given the importance of using an RCT to establish the impact of different levels of oxygen saturation from birth on short and long term growth, recognizing the wealth of oxygen saturation data that will be available for analysis and the absence of comparable data in the literature, all infants in the SUPPORT Trial should be recruited into this secondary (n=1320). This sample size will be adequate to detect subtle differences in growth between the two groups with adequate (>=80%) power. For example, this sample size will have at least 80% power to detect a difference in means between the two saturation groups of less than 40 g (assuming a mean weight of 1000 g in the control group and a standard deviation of 250 g) using a two group t-test with a 0.05 two-sided significance level.

Statistical Analysis:

Based upon intent-to-treat, differences between treatment arms with respect to continuous outcomes (such as weight, length, etc.) will be assessed by the Student t-test or the Mann-Whitney U-test, depending upon whether the empirical distribution of the data is approximately normal or heavily skewed. Adjusted analyses will be conducted using linear regression to determine the relationship between measures of oxygen saturation

and growth in the presence of covariates and confounders (such as site, gestational age, gender, etc.). Categorical outcomes (such as BPD, growth failure, etc.) will be compared across treatment groups using the chi-square test. Logistic regression models will be developed to determine whether oxygen saturation independently affects growth after correction for confounding variables that also alter growth.

Under all options of data collection, in-hospital growth data will be available over multiple points in time (under option 1, we are admittedly limited to only 2 time points after birth and sophisticated longitudinal modeling may not be worthwhile in that situation). Outcomes available on such a temporal scale enable us to contemplate a longitudinal analysis comparing the trajectories of growth between the two treatment groups. Longitudinal studies are usually more powerful than cross-sectional studies, both in terms of explanatory power and statistical efficiency. They are useful in examining whether children in the two different oxygen saturation arms have different developmental trajectories over time. Further, longitudinal studies are statistically more efficient since they acknowledge and account for naturally occurring differences among children, including unmeasured characteristics such as genetic make-up, prenatal exposures, etc.

In order to analyze longitudinal growth data we propose to use hierarchical modeling, where the first stage models growth as a function of time/child's age, and the second stage models this association as a function of each child's treatment status. This flexible modeling formulation allows each child to have its own unique developmental trajectory, which could depend on its treatment status.

Discussion of Anticipated Results

We anticipate a better growth outcome in-hospital and at 18-22 months corrected age in the infants randomized to the lower target saturation range who maintained their median oxygen saturations within study range. We further anticipate that longitudinal analyses, if feasible, will demonstrate that these infants will have a sustained higher trajectory of growth over time compared to infants in the higher target saturation range.

Budget:
OPTION 1:
No additional costs to implement study

OPTION 2:
Assuming 35% mortality for this extremely preterm population, estimated from GDB, additional nursing time is estimated to be 15-30 minutes and the total cost for 858 subjects surviving to discharge, whose data will be collected by chart review at discharge and at follow-up, is $6,864.00-$13,728.00

OPTION 3:
Time needed by research nurses to review subject records and collect additional anthropometric and nutritional data. Costs for 858 subjects surviving to discharge @ 2-3 hours/subject =$54,912.00-$82,368.00

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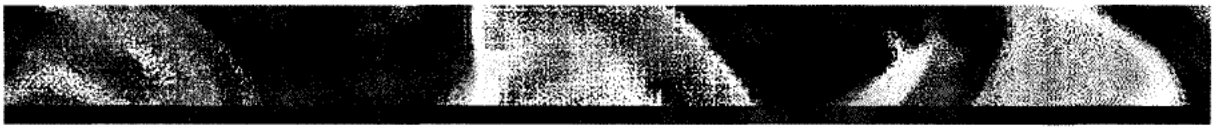
From: William Oh
To: WCarlo@peds.uab.edu; goldb008@mc.duke.edu; mazie_tinsley@oz.ped.emory.edu; Abbot Laptook
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: secondary to support trial
Date: Tuesday, July 05, 2005 7:42:09 AM
Attachments: .msg
fluid support secondary.doc

Blansfield, Earl (NIH/NICHD) [E]



Good morning everyone: You may recall that during the Steering Committee meeting I indicated that it might be important to take the opportunity of collecting weight loss, fluid and sodium intakes data on infants randomized in SUPPORT trial to confirm the hypothesis that we tried so hard in the writing of the sodium and fluid restriction protocol. I put together a proposal for submission to the SUPPORT subcomittee for consdieration. Since you folks were so instrumental in putting the fluid restriction protocol together, I would like to include you as the work group in putting this protocol together. I would appreciate your taking a little time out of your busy schedule to give me your inputs.

Thanks

Bill

July 4, 2005 draft

Postnatal Weight Loss during the first week of life and risk of Bronchopulmonary Dysplasia in Very Low Birth Weight Infants

A Secondary Study to the SUPPORT Trial

William Oh, MD and Sodium restriction working group (Wally Carlo,MD.Ronald Goldg=berg,MD, Barbara Stoll,MD and Abbot Laptook,MD)

Statement of the Problem

Bronchopulmonary Dysplasia (BPD) is a multifactorial disease affecting primarily the very low birth weight infants. Prematurity, oxygen exposure, volutrauma and inflammation have been shown to play important roles in its pathogenesis [1]. There is also evidence that excessive fluid and sodium intakes resulting in lack of contraction of extracellular fluid may play a role [2-4]. The lack of contraction of ECF is reflected in the lack of postnatal weight loss during the first week of life [5,6] which in turn has been shown to be associated with a higher incidence of BPD [7]. The rationale is that lack of normal physiologic contraction of ECF (reflected by lack of appropriate postnatal weight loss) leads to retention of fluid in the pulmonary interstitial tissue which lowers the lung compliance requiring an increase needs for oxygen and assisted ventilation. Based on this theory The SUPPORT trial was designed to test the hypothesis that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks. The factorial design also allows for the testing

of another hypothesis. i.e. relative to infants managed with a higher SpO2 range that the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the ccurrence of threshold ROP and/or the need for surgical intervention. The primary outcome of the first hypothesis is BPD and is based on the rationale that avoiding mechanical ventilation and intubation will reduce the incidence of BPD. The study offers a window of opportunity to test the hypothesis that excessive fluid and sodium intakes results in the lack of appropriate contraction of ECF reflected by lack of appropriate weight loss. The lack of appropriate physiologic transition with reference to body fluid adjustment will result in pulmonary interstitial fluid retention, lower lung compliance and needs for more oxygen therapy and assisted ventilation, leading to increased risk for BPD. Successful verification of our hypothesis will offer evidence that appropriate fluid and sodium therapy to assure normal physiologic transition will further reduce the incidence of BPD and its serious co-morbidities.

Background

BPD, defined as oxygen dependence at 36 completed post-conceptual age is the most common morbidity among ELBW survivors. This complication has a significant impact on the care of these infants during the first few years of life since it is associated with significant respiratory morbidities during the first year [8] Our Network data also showed that BPD is a predictor for neuro-developmental impairment at 18-22 months of age [9] Therefore, the reduction of this complication among ELBW survivors is clinically relevant and important.

The pathogenesis of BPD is multi-factorial and is a combination of prematurity, oxygen toxicity, volu or barotrauma, inflammation, and micro aspiration [1] A common denominator of these factors is the need for oxygen therapy and assisted mechanical ventilation during the early neonatal period as a result of pulmonary pathology, It is also possible that fluid retention may add to the problem of reduced lung compliance.Another probable cause of BPD is the inappropriate fluid and electrolyte therapy in this high-risk population during the early postnatal period. This is the subject of the current proposal.

In ELBW infants, the body water content is very high and a large proportion of it is in the extracellular (ECF) compartment [10,11]. During the first week of life, for a yet unknown mechanism, there is a physiologic contraction of the ECF associated with corresponding amount of weight loss [12,13].The peak period of contraction and associated weight loss appear to be within the first 7 days of life. The contraction of ECF is a physiologic phenomenon occurring at a time when infants have diuresis, and, in those with respiratory distress, improvement of pulmonary function [14]. The contraction of ECF is also associated with weight loss during the first week of life representing the amount of fluid being excreted through the kidney [12]. This physiologic process may not occur if excessive fluid and or sodium administration were given during the critical period.

High fluid intake with persistent expanded ECF is associated with a higher incidence of symptomatic patent ductus arteriosus (PDA) [15], and necrotizing enterocolitis (NEC) [16]. There is also suggestive evidence that PDA is associated with an increased incidence of BPD [17]. It is possible that, with the retention of

ECF and the presence of PDA with left-to-right shunt, there may be a higher fluid content in the pulmonary interstitial tissue leading to lower lung compliance and necessitate greater respiratory support in the form of oxygen administration and mechanical ventilation. The latter may result in lung injury and BPD.

Two studies have shown that, when fluid intake in the first week of life is too high, significant body fluid retention occurs, resulting in a higher incidence of oxygen dependence at 28 days and 36 completed conceptual weeks [18,19]. In one study, Van Marter et al [18] performed a retrospective case control analysis of infants with or without BPD, defined as oxygen dependence at 28 days. The result showed that the group of infants with BPD has a hgher crystalloid and colloid intakes during the first week when compared with the group without BPD. The BPD group also has a significantly lower postnatal weight loss. This study has limitations in that 1) it was a retrospective analysis, 2) comfounding variables such as birth weight and gestational age were not considered in the analysis intake and 3) the end point (BPD) was defined as oxygen dependence at 28 days of age.

The other study [19] is a retrospective analysis of the fluid intake data from our own Glutamine trial that shows statistical association between high fluid intake and less postnatal weight loss and increased risk of death or BPD. A recent Cochrane review performed by Bell and Acarregui [20] cited two additional RCTs [21,22] that examines the effects of restricted fluid intake during the first week of life in very low birth infants. They concluded that there is a trend of lower incidence of BPD when fluid intake was restricted but none of the studies reached

statistical significance. The Meta analysis shows a trend toward reduction of BPD (OR 0.70, 95% CI 0.42-1.22). They concluded that a research priority is to examine the impact of fluid intake on morbidity such as BPD in the ELBW infants.

Two studies documented the effect of sodium restriction on the incidence of BPD. One study was a randomized control trial conducted by Costarino et al.[23] They randomized infants with birth weight <1,000 grams or <28weeks into early sodium supplementation, 3 mEq /kg/day starting on day 1,n=9 and a late supplementation group, 3-4 mEq/kg/day starting on day 6,n=8. The result showed that the early supplemented group has positive sodium balance and higher incidence of BPD (oxygen dependence at 28 days) when compared with the late supplementation group. The limitation of this study is apparent in that the number is very small and the definition of BPD is not contemporary. Hartnoll et al [24] recently published the results of RCT involving infants with a gestational age of 25-30 weeks. The infants were randomized into early (n=24) or delayed (n=22) sodium supplementation group Early group received parenteral sodium supplementation (4 mM/kg/day) on day 2 of life while the delayed group received similar amount of sodium supplementation when 6% weight loss was achieved. The results show that the delayed sodium supplementation group has a lower incidence of oxygen dependence (26, 22 and 16% difference on day 7 day, 28 day and 36 completed weeks respectively when compared with the group who received early sodium supplementation. Because of sample size limitation, the difference is significantly only on day 7 p<.03). The authors also measured total and extracellular body fluid in the studied infants [25]. They showed that the

delayed sodium supplementation group has greater reduction in total and extracellular body fluid when compared with the early supplemented group.

These data suggest that fluid and electrolyte balance can be an important factor in the pathogenesis of BPD, probably because of lower pulmonary compliance as a result of fluid retention and the need for longer ventilatory assistance and oxygen therapy. An important element in producing body fluid retention in the first week of life is either excessive fluid intake or excessive sodium intake. The latter produces a positive sodium balance and its concomitant fluid retention. It is a well-known physiologic principle that positive sodium balance of one mEq of sodium will result in the net retention of 6.7 mL of fluid, primarily in the extracellular fluid space.

Hypothesis

Primary hypothesis Appropriate weight loss of > 6% of birth weight during the first 7 days of life will contribute to a reduction of the incidence of BPD by 5% of the expected event rate in the SUPPORT trial ; inappropriate weight loss of < 5% of birth weight during the first week will increase the incidence of BPD by 5 % above the expected rate predicted in the SUPPORT trial

Secondary Hypothesis Appropriate or inappropriate postnatal weight loss, as defined in this protocol is related to fluid and sodium intake. The former is a result of appropriate amount of fluid and sodium administered during the first week and the latter is due to excessive fluid and sodium administered during the first seven days.

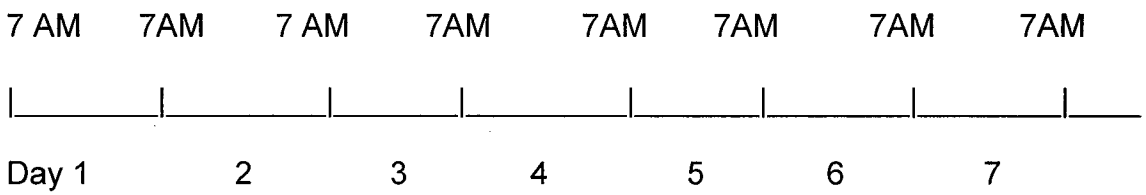
Specific Aims

1. Design a data collection form to prospectively record the daily weight changes and fluid and sodium intake during the first week of life for each infant randomized into the SUPPORT trial
2. Develop a priori a designated group of randomized infants who have appropriate weight loss of > 6% of birth weight; another group will be those who have inappropriate weight loss (<5% of birth weight).
3. When the primary SUPPORT trial is completed, data will be analyzed to test the hypothesis that randomized infants with appropriate weight loss will have a lower incidence of death or BPD than those with inappropriate weight changes in the respective randomized cohort. The primary measure for grouping is weight changes because it reflects the changes in ECF as a consequence of fluid and sodium intakes during the critical period of physiologic transition during the first week of life. The fluid and sodium intake data will verify the association of weight changes, ECF status as a result of appropriate or excessive fluid and sodium administration.

Methods

The fluid and electrolyte management of the randomized infants will be at the discretion of the attending clinicians. The data collection for this secondary study will be done only during the first week of life. To maintain consistency of data collection with reference to age, the first 7 days will consist of seven-24 hours

windows using 7 AM each day as the 0 hour for the day as shown in the figure below.



Data collection will begin at first 7AM after birth. This time frame will work best with inborn infants who are the primary subjects of the SUPPORT trial.

- For body weight, day 1 will be weight obtained at birth; for subsequent age in day, the weight obtained during the corresponding 24 hour window will be recorded. If the infant has more than one weight, the lowest weight will be recorded.

- For fluid and sodium intake, the amount given during each 24 hour window will be totaled to represent the daily intake

  The fluid and sodium intakes will include those that were prescribed by the clinicians as the daily maintenance intake (intended) and those that were given in conjunction with 'line flushing' during blood withdrawal or medication administration as well as those given as 'bolus' infusion for clinical reasons. These values will be termed 'unintended'

  Enteral fluid and sodium intakes will be minimal during the first 7 days and will not be recorded to minimize work load..

Data analysis

At the end of the main trial, the weight, fluid and sodium intake data will be analyzed as follow:

The randomized infants will be categorized into two groups based on the maximum weight loss during the first week of life.

Group 1 Appropriate weight loss - maximal weight loss > 6% of birth weight

Group 2 Inappropriate weight loss- maximal weight loss < 5% of birth weight and those infants who did not experience weight loss Infant with weight loss between 5 and 6 % will be rounded up by a conventional method.

The data will be analyzed as follow:

Primary analysis: Using death or BPD as primary outcome, the data will be analyzed using the format shown in the table below:

Table 1

Main trial grouping	Early CPAP		Prophylactic/early surfactant	
Secondary study grouping	Appropriate weight loss	Inappropriate Weight loss	Appropriate weight loss	Inappropriate Weight loss
Predicted death or BPD rate	+	++	++	+++

+ Lowest rate
++ Intermediate rate
+++ Highest rate

Secondary Analysis: The fluid and sodium intakes will be analyzed using the format shown in the table below:

Table 2

Parameter	Fluid intake (mL/kg/day		Sodium intake (mEq/kg/day)	
Group	Appropriate weight loss	Inappropriate Weight loss	Appropriate weight loss	Inappropriate Weight loss
Predicted outcome	Low	High	Low	High

Tertiary analysis

Further analysis will be done to compare the outcomes of the two secondary study groups (appropriate and inappropriate weight loss) with reference to some of the secondary outcomes being considered by the main trials. When compared with infants having inappropriate weight loss, the group with appropriate weight loss will have:

A decrease of the total duration of mechanical ventilation during the entire NICU stay

A decreased incidence of surfactant treatment

□A decreased incidence of air leaks on admission and overall

□A decreased duration of intubation

□A decreased duration of mechanical ventilation

□A decreased duration of oxygen supplementation

□□A decreased incidence of blindness of at least one eye at 18-22 month follow-up

□A decrease in the percentage of infants who receive postnatal steroids to prevent or treat BPD

□A decreased incidence of BPD at 36 weeks using the physiologic definition of BPD

□

□A decreased incidence of neurodevelopmental impairment at 18-22 month

□A decreased incidence of cerebral palsy at 18-22 month

Risk/Benefits None

Sample size

Analysis of glutamine trial data performed by Lisa Wrage shows that 72% of randomized infants (BW < 1,000 g) has weight loss > 6% and 28% has weight loss of <5% of birth weight during the first seven days. Data analysis also shows that those with appropriate weight loss (>6% of birth weight) has an event rate for death or BPD of 63% vs. the event rate of 53% (a difference of 9%) for those who did not have appropriate weight loss(<5% of birth weight). Therefore, our projection is that appropriate or inappropriate weight loss reflecting the appropriateness of fluid and sodium therapy will add a 9% reduction in death or BPD rate (4.5% In each stratum); or conversely, a 9% worse outcome of event rate over and above the rate projected by SUPPORT trial. Thus, if we implement this secondary protocol to capture 1,310 randomized infants in the SUPPORT trial, the projected number of infants in each cell and power of the assumed differences in the event rate for death or BPD will be as follow:

Table 3

Main trial grouping	Treatment		Control	
Death or BPD	58%		68%	
Secondary study group	Appropriate weight loss	Inappropriate weight loss	Appropriate weight loss	Inappropriate weight loss
Death or BPD	53%	63%	63%	73
Potential n	468	182	468	182
Power for 1 sided p value	81%		81%	
Power for 2 Sided p value	72%		72%	

Thus, if the reduction is indeed similar to the glutamine trial, the preset sample size by SUPPORT trial will only allow us to confirm the hypothesis with a limited power (80% with one sided p value. If the reduction rate due to appropriate fluid therapy is higher than projected (5%), then the power will improve.

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From: Abbot Laptook
To: Duara, Shahnaz; Neil Finer
Cc: Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; Higgins, Rosemary (NIH/NICHD) [E]; Ken Poole; Michele; Shahnaz Duara; Wade Rich; Wally Carlo; Daniel Gingras; Angelita Hensman
Subject: RE: support
Date: Saturday, July 02, 2005 5:03:25 PM

Neil, Shahnaz
We only recently got the Dragers for the purpose of using them to provide SIMV since will not be able to maintain our fleet of Bear Cub 750s in the near future. Once our faculty saw the volume gaurantee mode it is being used selectively. We do not have set criteria for extubation from this mode since we don't have a fair amount of experience with it yet. AL

From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Saturday, July 02, 2005 4:26 PM
To: Neil Finer; Abbot Laptook
Cc: Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; higginsr@mail.nih.gov; Ken Poole; Michele; Shahnaz Duara; Wade Rich; Wally Carlo
Subject: RE: support

Hi,

My question to Abbott would be " How do babies at Brown normally get extubated from volume guarantee and A/C? Directly, or do they go to SIMV before coming off?" If they do the former, we may need to add a weaning step to SIMV, followed by rate weans in a technical memo. I don't know how you would decide which breaths to ignore in an A/C mode, since the set rate is only a back up rate, designed to kick in when babies become apneic or breathe below the back up rate.

Shahnaz

> -----Original Message-----
> **From:** Neil Finer [mailto:nfiner@ucsd.edu]
> **Sent:** Saturday, July 02, 2005 4:14 PM
> **To:** 'Abbot Laptook'
> **Cc:** 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
> **Subject:** RE: support
>
> Hi Abbot
> In this situation I agree that one approach would be to return to a more conventional mode. The use of assist/control will provide some ventilator assist at each breath, and so the other option is to ignore the Assist/control breaths, as opposed to turning off this mode. It was and is the intent of the protocol to provide reasonable and frequently used extubation criteria. I understand that the use of assist/control may be delaying extubation in some infants. A literal reading of the protocol would suggest that we use the actual set ventilator rate, as there was no mention of assist/control breaths. In addition, the use of assist control may increase the MAP > than threshold. Whatever is done should be done to all infants for consistency. I will place this on the Agenda for our next call
> Thanks
> Neil
>
> ---
>
> **From:** Abbot Laptook [mailto:ALaptook@WIHRI.org]
> **Sent:** Friday, July 01, 2005 12:15 PM
> **To:** nfiner@ucsd.edu
> **Subject:** FW: support

Neil
any thoughts on the issue below? Abbot

From: Angelita Hensman
Sent: Friday, July 01, 2005 10:43 AM
To: Abbot Laptook
Subject: RE: support

I think there is a SUPPORT subcommittee conference call coming up soon. May be you could send them this e-mail to see what the other sites are doing in this situation?
Angelita

From: Abbot Laptook
Sent: Friday, July 01, 2005 10:36 AM
To: Daniel Gingras
Cc: Angelita Hensman; Kim Francis
Subject: support

Dan
In discussing the support trial with the new housestaff, one of the PL-2 asked how does an infant meet extubation criteria if they are on the drager in the volume gaurantee mode with assistant control. I doubt that any infant in this mode will meet the rate requirement of less than or equal to 20bpm. My suggestion was if they wanted to use volume gaurantee, to use this mode and attempt to wean. Once at settings that they felt comfortable with extubation, switch back to SIMV and make sure the infant meets the rate criteria. Sounds reasonable? AL

From:	Wally Carlo, M.D.
To:	Duara, Shahnaz; Neil Finer; Abbot Laptook
Cc:	Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; Higgins, Rosemary (NIH/NICHD) [E]; Ken Poole; Michele; Shahnaz Duara; Wade Rich
Subject:	RE: support
Date:	Saturday, July 02, 2005 4:31:56 PM

Hi: I agree with Shane's points. Wally

From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Saturday, July 02, 2005 3:26 PM
To: Neil Finer; Abbot Laptook
Cc: Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; higginsr@mail.nih.gov; Ken Poole; Michele; Shahnaz Duara; Wade Rich; Wally Carlo, M.D.
Subject: RE: support

Hi,

My question to Abbott would be " How do babies at Brown normally get extubated from volume guarantee and A/C? Directly, or do they go to SIMV before coming off?" If they do the former, we may need to add a weaning step to SIMV, followed by rate weans in a technical memo. I don't know how you would decide which breaths to ignore in an A/C mode, since the set rate is only a back up rate, designed to kick in when babies become apneic or breathe below the back up rate.

Shahnaz

> -----Original Message-----
> **From:** Neil Finer [mailto:nfiner@ucsd.edu]
> **Sent:** Saturday, July 02, 2005 4:14 PM
> **To:** 'Abbot Laptook'
> **Cc:** 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
> **Subject:** RE: support
>
> Hi Abbot
> In this situation I agree that one approach would be to return to a more conventional mode. The use of assist/control will provide some ventilator assist at each breath, and so the other option is to ignore the Assist/control breaths, as opposed to turning off this mode. It was and is the intent of the protocol to provide reasonable and frequently used extubation criteria. I understand that the use of assist/control may be delaying extubation in some infants. A literal reading of the protocol would suggest that we use the actual set ventilator rate, as there was no mention of assist/control breaths. In addition, the use of assist control may increase the MAP > than threshold. Whatever is done should be done to all infants for consistency. I will place this on the Agenda for our next call
> Thanks
> Neil
>
> ---
>
> **From:** Abbot Laptook [mailto:ALaptook@WIHRI.org]
> **Sent:** Friday, July 01, 2005 12:15 PM
> **To:** nfiner@ucsd.edu
> **Subject:** FW: support
>
> Neil
> any thoughts on the issue below? Abbot
>
> ---
>
> **From:** Angelita Hensman

Sent: Friday, July 01, 2005 10:43 AM
To: Abbot Laptook
Subject: RE: support

I think there is a SUPPORT subcommittee conference call coming up soon. May be you could send them this e-mail to see what the other sites are doing in this situation?
Angelita

From: Abbot Laptook
Sent: Friday, July 01, 2005 10:36 AM
To: Daniel Gingras
Cc: Angelita Hensman; Kim Francis
Subject: support

Dan
In discussing the support trial with the new housestaff, one of the PL-2 asked how does an infant meet extubation criteria if they are on the drager in the volume gaurantee mode with assistant control. I doubt that any infant in this mode will meet the rate requirement of less than or equal to 20bpm. My suggestion was if they wanted to use volume gaurantee, to use this mode and attempt to wean. Once at settings that they felt comfortable with extubation, switch back to SIMV and make sure the infant meets the rate criteria. Sounds reasonable? AL

From: JANET MORGAN
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Roy Heyne
Subject: Support Study Follow-up Questionnaire
Date: Friday, July 01, 2005 4:49:56 PM

Rose,
I had a few questions regarding the interviews done at 6,12, 18 months and discharge. On the 6,12 and 18 month interviews the question #18 asked about pets but does not specify indoors or out, the discharge interview separates indoor from outdoors pets. Do we assume that after discharge that question is not as important. I am unsure of who I would ask the questions on the last page of the appendix. The questions ask for name, relationship, age, sex and several other questions ,but I did not understand who to ask these question. I appreciate your help with these questions so we will be on target with the first study patients.

Thanks,
Janet Morgan

From: Roy Heyne
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: JANET MORGAN
Subject: Re: FW: Pulmonary outcomes secondary study
Date: Friday, July 01, 2005 4:14:21 PM

Sorry, Rose, I thought we had already responded, since Janet and I had already discussed and decided on the local rather than the Rochester option. Given the nature of our population, we think we think our patients are much more likely to cooperate with interviews by people whom they can identify with the care team they have seen than with strangers over the phone.

By the way, we are still operating on the assumption that we can do the baseline questionnaire on first clinic visit after discharge rather than pre-discharge (as we do for the PCV7 study), though I have not yet gotten a reply from the support group to that question. Janet has also raised a number of other points on the questionnaire that could use some further clarification and will forward those on.

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 06/29/05 2:10 PM >>>
Hi

Can you send me your preference for the administration of the questionnaires
for the Pulmonary Follow up study to SUUPPORT?
Thanks

Rose

From: Higgins, Rosemary (NIH/NICHD)
Sent: Friday, June 17, 2005 10:07 AM
To: Abbot Laptook (alaptook@WIHRI.org); 'Abhik Das'; 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; 'Charles Rosenfeld'; 'Dale Phelps'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; 'Jobe Alan (E-mail)'; 'Lemons Jim (E-mail)'; 'Michael O'Shea'; 'Michelle Walsh'; 'Neil Finer'; 'Oh William (E-mail)'; 'Poole Kenneth (E-mail)'; 'Ronald GOldberg'; 'Shahnaz Duara'; 'Shankaran Seetha (E-mail)'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; Walid Salhab (Walid Salhab); Anna Dusick (adusick@iupui.edu); Betty Vohr ('Betty_Vohr@brown.edu'); Charlie Bauer (cbauer@peds.med.miami.edu); Dee WIlson ((b) (6) Gary Myers (Gary_myers@URMC.Rochester.edu); 'Ira Adams-Chapman'; Jean Steichen (steichjj@email.uc.edu); Myriam Peralta (mperalta@peds.uab.edu); Ricki Goldstein (golds005@mc.duke.edu); 'Robert Dillard'; 'Roy Heyne'; 'Susan Hintz'; Yvette Johnson (yjohnson@med.wayne.edu); Yvonne Vaucher (Yvonne Vaucher)
Cc: 'Hastings, Betty J.'; (kzaterka@rti.org); 'Petrie, Carolyn'
Subject: Pulmonary outcomes secondary study

Hi

Attached are documents and questionnaires associated with the pulmonary

outcomes secondary study to the SUPPORT Trial. Please review the documents and send me a preference by June 27 indicating the following:

1. My site will do the Questionnaires

2. Rochester site to do questionnaires on my study subjects

I am checking on the issues regarding how the consents would be phrased in order that information could pass from your site to the Rochester site.

Thanks in advance for all your help!!
Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

From: Higgins, Rosemary (NIH/NICHD)
To: Petrie, Carolyn; Richard Ehrenkranz
Subject: RE: protocol review: probiotics & growth secondary to support
Date: Friday, July 01, 2005 9:53:00 AM

They are having a call today - bill will send the new protocol next week.
Thanks
Rose

-----Original Message-----
From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Friday, July 01, 2005 9:53 AM
To: Richard Ehrenkranz
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: RE: protocol review: probiotics & growth secondary to support

I will resend to the group. The June 22 is the most recent version that
I have. Please let me know if there is a more current one.

-----Original Message-----
From: Richard Ehrenkranz [mailto:richard.ehrenkranz@yale.edu]
Sent: Friday, July 01, 2005 9:51 AM
To: Petrie, Carolyn
Subject: Re: protocol review: probiotics & growth secondary to support

Carolyn:
Have we received the revised probiotics protocol yet? I will send out
the
growth protocol and assign reviewers.
Richard

At 05:31 PM 6/30/2005, you wrote:
>
>The protocol review conference call to discuss the protocols:
>* Probiotics
>* Growth secondary to SUPPORT
>Is scheduled for:
>
>Thursday, August 4
>3:00-5:00pm ET
>
>To join the call:
>Dial Tollfree: 866-675-3256
>Passcode: 560152 (# when prompted)
>
>Leader: Rose Higgins

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

From: Higgins, Rosemary (NIH/NICHD)
To: "petrie@rti.org"
Subject: Fw: growth prot June 30 2005.doc
Date: Thursday, June 30, 2005 1:04:54 PM
Attachments: growth prot June 30 2005.doc

We wil likely need 2 hours for the protocol review call.

This one + probiotics!

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Duara, Shahnaz <SDuara@med.miami.edu>
To: richard.ehrenkranz@yale.edu <richard.ehrenkranz@yale.edu>
CC: Neil Finer <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Thu Jun 30 13:02:18 2005
Subject: growth prot June 30 2005.doc

Hi Rich,

I wish to submit the Growth secondary to SUPPORT for protocol review on Cristina Navarrete's behalf. She has developed 3 scenarios of data collection, with input from Abhik, and matching budgets.

Look forward to the response from your committee.
Shahnaz
<<growth prot June 30 2005.doc>>

Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study: A Proposed Secondary Study

Cristina Navarrete MD, and Shahnaz Duara MD
University of Miami Miller School of Medicine, Miami, FL.

Abstract:

Post-natal growth restriction is a major problem in preterm infants. Perturbations in oxygenation are recognized to influence post-natal growth; hypoxic conditions can directly impair growth and hyperoxic conditions predispose infants to BPD, which in turn has been linked to poor growth. The NICHD Neonatal Network is conducting a prospective trial of preterm infants randomized to two levels of baseline oxygen saturations. The effect of baseline saturations on pulmonary morbidity and ROP are the primary outcome measures. With respect to post-natal growth, there is a paucity of data relating alterations in baseline oxygen saturation and/or frequent deviations above or below the baseline to growth outcomes. We propose a secondary study to quantify short-term growth velocity in-hospital and long-term growth at 18-22 months of corrected age for infants enrolled in the SUPPORT Trial in relationship to oxygen saturation.

A. Hypothesis to be tested

Primary:

1. Infants in the low oxygen saturation group (85-89%) will have better in-hospital and better long-term (18-22 months corrected age) growth. If growth data are available at multiple time points in the in-hospital period, then we hypothesize that trajectories of growth in hospital will be better for infants in the low oxygen saturation group.

Secondary:

1. Growth will be greater in infants who spend > 50% of the time with daily median oxygen saturation between 85% -95% while on supplemental oxygen, independent of randomization to low or high oxygen saturation.

2. Infants with BPD will have poorer in-hospital and long-term growth than infants without BPD, independent of randomization to low or high oxygen saturation.

3. Long-term growth will be positively related to neuro-developmental outcome, independent of randomization to low or high oxygen saturation.

B. Specific Aims:

1. To determine anthropometric measurements (wt, HC, length) in infants randomized to low and high oxygen saturation arms, from birth to hospital discharge and again at 18-22 months corrected age.
2. To determine nutritional intake (parenteral and enteral) during hospital stay.
3. To determine the percentage of infants with growth <10 percentile at 36 weeks PMA or discharge, whichever comes first.
4. To determine the percentage of infants with growth <10 percentile at 18-22 months corrected age.
5. To determine growth in relation to the proportion of time spent with oxygen saturation
    a. <85% and >95%
    b. 85-95%
6. To determine growth in relation to the proportion of infants with
    a. median oxygen saturation > 95%
    b. median oxygen saturation 75% - 84%
    c. median oxygen saturation < 75%
7. To relate incidence of BPD in low and high saturation arms to growth.
8. To determine in-hospital growth velocity/trajectory in low and high saturation arms.
9. To determine long-term growth velocity/trajectory, from hospital discharge to follow up at 18-22 months corrected age in low and high saturation arms.
10. To relate neuro-developmental outcome at 18-22 months corrected age to long-term growth in low and high saturation arms.

Rationale:

The SUPPORT Trial will randomize infants to two ranges of SpO2 in order to test the hypothesis that use of a lower SpO2 range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity and/or the need for surgical intervention. Retrospective cohort data from several units in the U.K., with different oxygen supplementation policies, revealed poorer growth patterns in the preterm infants exposed to higher oxygen saturations for the duration of oxygen exposure (Tin 2001). Conversely, observational data of infants with established BPD show better growth with home oxygen support (Groothius 1987), and two recent RCT of different target saturations in older oxygen-dependent premature infants showed no difference in short or long-term growth outcomes (STOP-ROP 2000, BOOST Trial 2003). There are no RCT data evaluating the short or long-term growth impact of different SpO2 strategies with supplemental oxygen use in a birth cohort of extremely preterm infants. Therefore, this study provides an opportunity for us to obtain critically needed growth information on premature infants who are exposed from birth to different target oxygen saturation strategies.

Background

Improvements in antenatal care, respiratory support and nutrition have contributed to increased survival of ELBW infants. As the number of survivors increase, the long term outcome of these infants becomes more important. Lemons et al described growth failure or weight <10th percentile at 36 weeks postmenstrual age in 97% of ELBW infants surviving to discharge. Some morbidities in adulthood are linked to growth during the early post-natal period (Singhal 2004) and make adequacy of growth in this population of heightened interest.

Instead of following intra-uterine growth curves of age matched fetuses, VLBW infants exhibit wide-spread post-natal growth retardation (Cooke 2004), losing ground during the first weeks of life (Berry 1997). To resume growth post-natally, nutrition is of paramount importance; however, other factors such as severity of illness and perhaps oxygenation also play a role. Observational studies of infants with BPD showed poor post-natal growth when infants were sent home without oxygen supplementation (Markestad 1981).

Although preterm infants without lung disease attain oxygen saturations >95%, artificial attempts to keep arterial oxygenation at a "physiological" level may not be beneficial to growth, the lung or retina (Tin 2001). Animal studies have shown that newborn mammals (mice, rats, guinea pigs) develop poor growth with chronic hypoxia and that blunted body growth is directly proportional to the profundity of the exposure to chronic hypoxia (Mortola 1990). Chronic hypoxemia has also been suggested as the cause of poor growth in patients with cyanotic congenital heart disease (Dundar 2000). When home oxygen supplementation was discontinued inappropriately by parents in a cohort of VLBW infants with BPD, there was a deceleration in the rate of weight gain, which improved when oxygen supplementation was resumed (Groothius 1987). Hudak et al in 1989 observed that ELBW infants with CLD who went home on oxygen supplementation had good catch-up growth at 19 months. Taken collectively, these data suggest that hypoxic conditions affect growth negatively and supplementing oxygen may improve growth.

The optimal level of oxygen saturation to promote post-natal growth is unknown. Most of the available human data is limited to oxygen supplementation of infants who are oxygen dependent or have BPD. Baraldi et al demonstrated that discharged infants with BPD, who were kept on supplemental oxygen to keep saturations above 94%, had progressive but poor weight gain (stayed below 3rd percentile) at 9 months corrected age follow-up. In infants with BPD whose oxygen supplementation was intentionally discontinued, the subset who exhibited episodes of desaturations below 88-91% had a significant decline in the rate of weight gain as compared to those who maintained saturations above 92% (Moyer-Mileur 1996). Conversely, when two different oxygen saturation control policies (high: 88-98% and low: 70-90%) were retrospectively reviewed in <28 week gestation infants, the infants being cared for in the high oxygen saturation policy units were more likely to weigh less than the 3rd percentile at discharge

(45% vs. 17%, Tin 2001). The infants assigned to the high oxygen saturation limits were also more likely to have BPD and ROP.

Recently, the BOOST Trial demonstrated that randomizing infants born <30 weeks gestation who were still on oxygen at 32 weeks postmenstrual age either to standard saturations (91-94%) or to high saturations (95-98%) produced no significant difference in growth at 12 months corrected age. This study, while randomizing infants to two different levels of saturations (conventional and high), only enrolled infants if they were still on oxygen supplementation at 32 weeks PMA and used higher limits than planned by SUPPORT. Our proposal is novel in that randomization to the two oxygen strategies begins at birth and continues for as long as the infants are in supplemental oxygen - by implementing this secondary we will be able to determine the impact of these strategies on short and long-term growth.

Methods:

OPTION 1: (basic GDB*data – current GDB)
Anthropometric Measures – at birth, 28 days, 36 weeks or discharge (wt, length, HC)
Clinical Data-

1. Date when infant regains birth weight
2. Date of first enteral feed
3. Date of full enteral feeds (enteral > 120ml/kg/d)
4. Total number of days on parenteral nutrition
5. Presence of BPD

OPTION 2: ('snapshots')
OPTION 1 plus additional anthropometric measures – weight, at postnatal days 7, 14, 21, and 32w PMA
Clinical Data – 24 h intake 'snapshots' (Parenteral, Enteral) – postnatal days 7, 14, 21, and 28, 32w PMA, 36w PMA or discharge (whichever comes first)

OPTION 3: (mimic glutamine dataset)
OPTION 1 plus:
Anthropometric Measures by study nurse (wt, length, HC) – weekly, until status
Clinical Data – 24 h intake (Parenteral, Enteral) – daily, until status

Intervention Data – (same for all OPTIONS)

1. Duration of time spent in target saturation ranges of interest (already part of SUPPORT‡)
2. Median values for unmasked oxygen saturation while still on supplemental oxygen therapy
3. Highest daily FiO2‡
4. Duration of supplemental oxygen exposure
5. Documentation of post-discharge oxygen use

Follow Up data – (same for all OPTIONS)

1. Anthropometric measurements at 18-22months corrected age
2. Neuro-developmental follow up at 18-22 months corrected age

Primary Outcome:

Growth in-hospital and at 18-22 months corrected age in high and low saturation arms.

Sample Size:

Given the importance of using an RCT to establish the impact of different levels of oxygen saturation from birth on short and long term growth, recognizing the wealth of oxygen saturation data that will be available for analysis and the absence of comparable data in the literature, all infants in the SUPPORT Trial should be recruited into this secondary (n=1320). This sample size will be adequate to detect subtle differences in growth between the two groups with adequate (>=80%) power. For example, this sample size will have at least 80% power to detect a difference in means between the two saturation groups of less than 40 g (assuming a mean weight of 1000 g in the control group and a standard deviation of 250 g) using a two group t-test with a 0.05 two-sided significance level.

Statistical Analysis:

Based upon intent-to-treat, differences between treatment arms with respect to continuous outcomes (such as weight, length, etc.) will be assessed by the Student t-test or the Mann-Whitney U-test, depending upon whether the empirical distribution of the data is approximately normal or heavily skewed. Adjusted analyses will be conducted using linear regression to determine the relationship between measures of oxygen saturation and growth in the presence of covariates and confounders (such as site, gestational age, gender, etc.). Categorical outcomes (such as BPD, growth failure, etc.) will be compared across treatment groups using the chi-square test. Logistic regression models will be developed to determine whether oxygen saturation independently affects growth after correction for confounding variables that also alter growth.

Under all options of data collection, in-hospital growth data will be available over multiple points in time (under option 1, we are admittedly limited to only 2 time points after birth and sophisticated longitudinal modeling may not be worthwhile in that situation). Outcomes available on such a temporal scale enable us to contemplate a longitudinal analysis comparing the trajectories of growth between the two treatment groups. Longitudinal studies are usually more powerful than cross-sectional studies, both in terms of explanatory power and statistical efficiency. They are useful in examining whether children in the two different oxygen saturation arms have different developmental trajectories over time. Further, longitudinal studies are statistically more efficient since they acknowledge and account for naturally occurring differences among children,

including unmeasured characteristics such as genetic make-up, prenatal exposures, etc.

In order to analyze longitudinal growth data we propose to use hierarchical modeling, where the first stage models growth as a function of time/child's age, and the second stage models this association as a function of each child's treatment status. This flexible modeling formulation allows each child to have its own unique developmental trajectory, which could depend on its treatment status.

Discussion of Anticipated Results

We anticipate a better growth outcome in-hospital and at 18-22 months corrected age in the infants randomized to the lower target saturation range who maintained their median oxygen saturations within study range. We further anticipate that longitudinal analyses, if feasible, will demonstrate that these infants will have a sustained higher trajectory of growth over time compared to infants in the higher target saturation range.

Budget:
OPTION 1:
No additional costs to implement study

OPTION 2:
Assuming 35% mortality for this extremely preterm population, estimated from GDB, additional nursing time is estimated to be 15-30 minutes and the total cost for 858 subjects surviving to discharge, whose data will be collected by chart review at discharge and at follow-up, is $6,864.00-$13,728.00

OPTION 3:
Time needed by research nurses to review subject records and collect additional anthropometric and nutritional data. Costs for 858 subjects surviving to discharge @ 2-3 hours/subject =$54,912.00-$82,368.00

References:

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From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Pulmonary outcomes secondary study
Date: Thursday, June 30, 2005 11:10:28 AM

Ellen is (b) (6) -- will talk to her
BJS"Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> on Thursday, June 30, 2005 at 9:54 AM +0000 wrote:
>Barbara
>There would need to be capitation either way - does that change your vote?
>Thanks
>Rose
>
>-----Original Message-----
>From: Barbara Stoll [mailto:barbara.stoll@oz.ped.emory.edu]
>Sent: Wednesday, June 29, 2005 5:22 PM
>To: Higgins, Rosemary (NIH/NICHD)
>Subject: Pulmonary outcomes secondary study
>
>We would prefer for the forms to be administered by Rochester. I assume
>there is no additional capitation for doing this.
>Thanks
>BJS
>
>Barbara J. Stoll, MD
>George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
>Medical Director, Children's Healthcare of Atlanta at Egleston
>Office: 404-727-2456 Fax: 404-727-5737
>barbara_stoll@oz.ped.emory.edu
>
>This message is for the designated recipient only and may contain
>privileged or confidential information. If you have received it in error,
>please notify the sender immediately and delete the original.

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
Medical Director, Children's Healthcare of Atlanta at Egleston
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

From: Neil Finer
To: "Wally Carlo, M.D."; Higgins, Rosemary (NIH/NICHD) [E]; "Wade Rich"; "Shahnaz Duara"; "Ed Donovan"; "Avroy A. Fanaroff, M.D."; "Michele Walsh-Sukys"; wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: O2 Saturation graphs
Date: Wednesday, June 29, 2005 4:20:36 AM

Hi Wally
I have reviewed these graphs and they are similar to what we discussed at the Steering Committee
Graph #1 would be clearer with the X axis labeled "Number of infants enrolled or enrolled per site"
as this could be used to see if there is a learning curve by number of infants enrolled. We would hope that the black and green increase at the expense of the others.
I like Graph #2 as site versus total
Graph # 3 – I would start the Xaxis at 50 or < 50% as the lower values are few and the graph is easier understood – at least to me.
I think that for the sites – graph#2 is the best.
These will be a great help.
I'm looking forward to the real data, I hope that it looks as good as your fictionary plots.
Be well
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, June 27, 2005 6:43 AM
To: Rose Higgins; Wade Rich; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.; Michele Walsh-Sukys; wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD)
Subject: O2 Saturation graphs

To Support Subcommittee:

Enclosed is attachment that addresses SUPPORT O2 saturation monitoring and compliance. We could discuss this during our next conference call. We discussed briefly at the Steering Committee, options to monitor compliance with the O2 saturation arm of the trial. I have put together several options of ways to analyze the data so we can provide feedback to the DSMB, the Subcommittee, and/or the investigators and colleagues. Please look at the various ways to represent data.

Thanks,
Wally

From: Brenda Poindexter
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Lemons, James A
Subject: Re: Pulmonary outcomes secondary study
Date: Wednesday, June 29, 2005 3:02:25 PM

Rose,
I'm sorry I missed your deadline – but our preference would be to have the Rochester site do questionnaires on study subjects. Not only would this work better for our site, but I think having a central site will decrease variability in how the questionnaire is administered and will reduce cost for the study as you would not need to train multiple groups of people.
Brenda

> Hi
> Attached are documents and questionnaires associated with the pulmonary outcomes secondary study to the SUPPORT Trial. Please review the documents and send me a preference by June 27 indicating the following:
> 1. My site will do the Questionnaires
>
>   1. Rochester site to do questionnaires on my study subjects
>
> I am checking on the issues regarding how the consents would be phrased in order that information could pass from your site to the Rochester site.
>
> Thanks in advance for all your help!!
> Rose

From: Michele Walsh
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich; Neil Finer; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.; Michele Walsh-Sukys
Subject: Re: O2 Saturation graphs
Date: Wednesday, June 29, 2005 12:40:43 PM

Wally:
I think the graphs will be very helpful. I would suggest making the pulse ox divisions match the Massimo histograms: >96, 93-96, 88-92, 84-87, and <84%.
I agree with starting fig 3 at 50%-100%.
FYI: we are still having trouble with the sats "swinging" from hyperoxia to hypoxia in those tiny infants who remain vent dependent.
Michele

----- Original Message -----
From: Wally Carlo, M.D.
To: Rose Higgins ; Wade Rich ; Neil Finer ; Wally Carlo, M.D. ; Shahnaz Duara ; Ed Donovan ; Avroy A. Fanaroff, M.D. ; Michele Walsh-Sukys ; wrich@ucsd.edu ; Higgins, Rosemary (NIH/NICHD)
Sent: Monday, June 27, 2005 9:43 AM
Subject: O2 Saturation graphs

To Support Subcommittee:

Enclosed is attachment that addresses SUPPORT O2 saturation monitoring and compliance. We could discuss this during our next conference call. We discussed briefly at the Steering Committee, options to monitor compliance with the O2 saturation arm of the trial. I have put together several options of ways to analyze the data so we can provide feedback to the DSMB, the Subcommittee, and/or the investigators and colleagues. Please look at the various ways to represent data.

Thanks,
Wally

From:	Neil Finer
To:	wrich@ucsd.edu
Cc:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wally Carlo"
Subject:	RE: SUPPORT
Date:	Tuesday, June 28, 2005 6:14:13 PM

Hi Nancy
Can you let me know why the IRB prohibits approaching Mom in labor Most of the time the Moms at 23 - 27 weeks are not having aggressive labor pains. Is the restriction related to the presence of other medications?
I am not as concerned about you getting dinged as the potentially low enrollment from you very active site. Is there the possibility to appeal this to the IRB since to my knowledge no other IRB has taken this position.
I would like to try to help if possible.
Thanks
Neil Finer

-----Original Message-----
From: Nancy Miller [mailto:Nancy.Miller@UTSouthwestern.edu]
Sent: Tuesday, June 28, 2005 10:53 AM
To: wrich@ucsd.edu
Subject: RE: SUPPORT

Wade,
Our IRB will not let us consent Moms in active labor. Do we add those too? Seems like we are going to get dinged a lot for Moms we can't consent.
Thanks
Nancy

>>> "Wade Rich" <wrich@ucsd.edu> 06/28/05 10:09 AM >>>
Nancy,
Everyone whom your OBs feel is at risk to deliver within the window should be screened.
Then, if they are eligible at the time of delivery but you have not consented them you fill out a SUPP02 eligibility form and say you did not consent them because personnel were not available.
Wade

-----Original Message-----
From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Tuesday, June 28, 2005 5:50 AM
To: wrich@ucsd.edu
Subject: FW: SUPPORT

Was this discussed and was there a decision made? I don't think so.
Please advise.

-----Original Message-----
From: Nancy Miller [mailto:Nancy.Miller@UTSouthwestern.edu]
Sent: Monday, June 27, 2005 4:51 PM
To: Hastings, Betty J.
Subject: Re: SUPPORT

Betty,

We started SUPPORT today and have a question. I remember some discussion about which Moms to put on the screening sheet and I didn't remember if we came to a decision. Since we aren't recruiting 24/7 I was just going to list the Moms we approached. Let me know if that sounds OK.

The second thing is Gay gave you one wrong number for the Pulse Ox's we sent off to UCSD. She gave you 311438 and it should have been 311384. The number for the second Pulse Ox is correct.

I guess that's about all for now.

Thanks,

Nancy

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; barbara.stoll@oz.ped.emory.edu
Subject: RE: SUPPORT
Date: Tuesday, June 28, 2005 6:11:01 PM

Thanks for the continuing enrollment Barbara
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 28, 2005 12:47 PM
To: Barbara Stoll; bkh@rti.org
Cc: Ann Blackwelder; nfiner@ucsd.edu
Subject: RE: SUPPORT

Barbara
Betty will help you with the numbers - keep up the good work!!
Rose

-----Original Message-----
From: Barbara Stoll [mailto:barbara.stoll@oz.ped.emory.edu]
Sent: Tuesday, June 28, 2005 3:47 PM
To: bkh@rti.org
Cc: Ann Blackwelder; Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT

Betty
I have a procedural question
We just enterred twins into SUPPORT. As per our understanding, they are to be randomized to the same group-- this time they randomized to mechanical ventilation NOT early CPAP.
The question is what randomization # to use. As a unit these twins are # 3002-- we put A and B
Should we use another #?
BJS

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
Medical Director, Children's Healthcare of Atlanta at Egleston
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

From: Duara, Shahnaz
To: Wally Carlo, M.D.
Cc: Neil Finer; Ed Donovan; Michele Walsh-Sukys; wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: O2 Saturation graphs
Date: Tuesday, June 28, 2005 5:33:27 PM

Hi Wally,

Graph 1 is not very clear to me - what is the X axis? There may be a lot of overlap of lines depending on how Y axis values cross each other.

Graphs 2 and 3 are fine. Depending on how frequently you plan to send graphs to sites, you may want to have group average and site average for both graphs.

Shahnaz

> -----Original Message-----
> **From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
> **Sent:** Monday, June 27, 2005 9:43 AM
> **To:** Rose Higgins; Wade Rich; Neil Finer; Wally Carlo, M.D.; Duara, Shahnaz; Ed Donovan; Avroy A. Fanaroff, M.D.; Michele Walsh-Sukys; wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD)
> **Subject:** O2 Saturation graphs
>
> To Support Subcommittee:
>
> Enclosed is attachment that addresses SUPPORT O2 saturation monitoring and compliance. We could discuss this during our next conference call. We discussed briefly at the Steering Committee, options to monitor compliance with the O2 saturation arm of the trial. I have put together several options of ways to analyze the data so we can provide feedback to the DSMB, the Subcommittee, and/or the investigators and colleagues. Please look at the various ways to represent data.
>
> Thanks,
> Wally

From: Hastings, Betty J.
To: Barbara Stoll
Cc: Ann Blackwelder; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Tuesday, June 28, 2005 4:17:43 PM

Barbara.
You are correct, the twins would be randomized to the same group. The randomization number (envelop) will be the same for both babies. Then as in GDB, the Network number is made up of a four digit Family (Pregnancy) Number plus the Birth Order Number (1 for first born, 2 for second, etc).
I hope this answers your question.
Betty

-----Original Message-----
From: Barbara Stoll [mailto:barbara.stoll@oz.ped.emory.edu]
Sent: Tuesday, June 28, 2005 3:47 PM
To: Hastings, Betty J.
Cc: Ann Blackwelder; higginsr@mail.nih.gov
Subject: SUPPORT

Betty
I have a procedural question
We just enterred twins into SUPPORT. As per our understanding, they are to be randomized to the same group-- this time they randomized to mechanical ventilation NOT early CPAP.
The question is what randomization # to use. As a unit these twins are #
(b) (6) we put A and B
Should we use another #?
BJS

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
Medical Director, Children's Healthcare of Atlanta at Egleston
Office: 404-727-2456 Fax: 404-727-5737 barbara_stoll@oz.ped.emory.edu

From: Higgins, Rosemary (NIH/NICHD)
To: Poole, W. Kenneth; bkh@rti.org
Subject: FW:
Date: Monday, June 27, 2005 12:39:00 PM

Ken and Betty
I think we need GDB forms for this baby in order to run SUPPORT analyses, correct?
Thanks
Rose

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Monday, June 27, 2005 12:37 PM
To: Higgins, Rosemary (NIH/NICHD)
Cc: nfiner@ucsd.edu; 'Michele Walsh'
Subject:

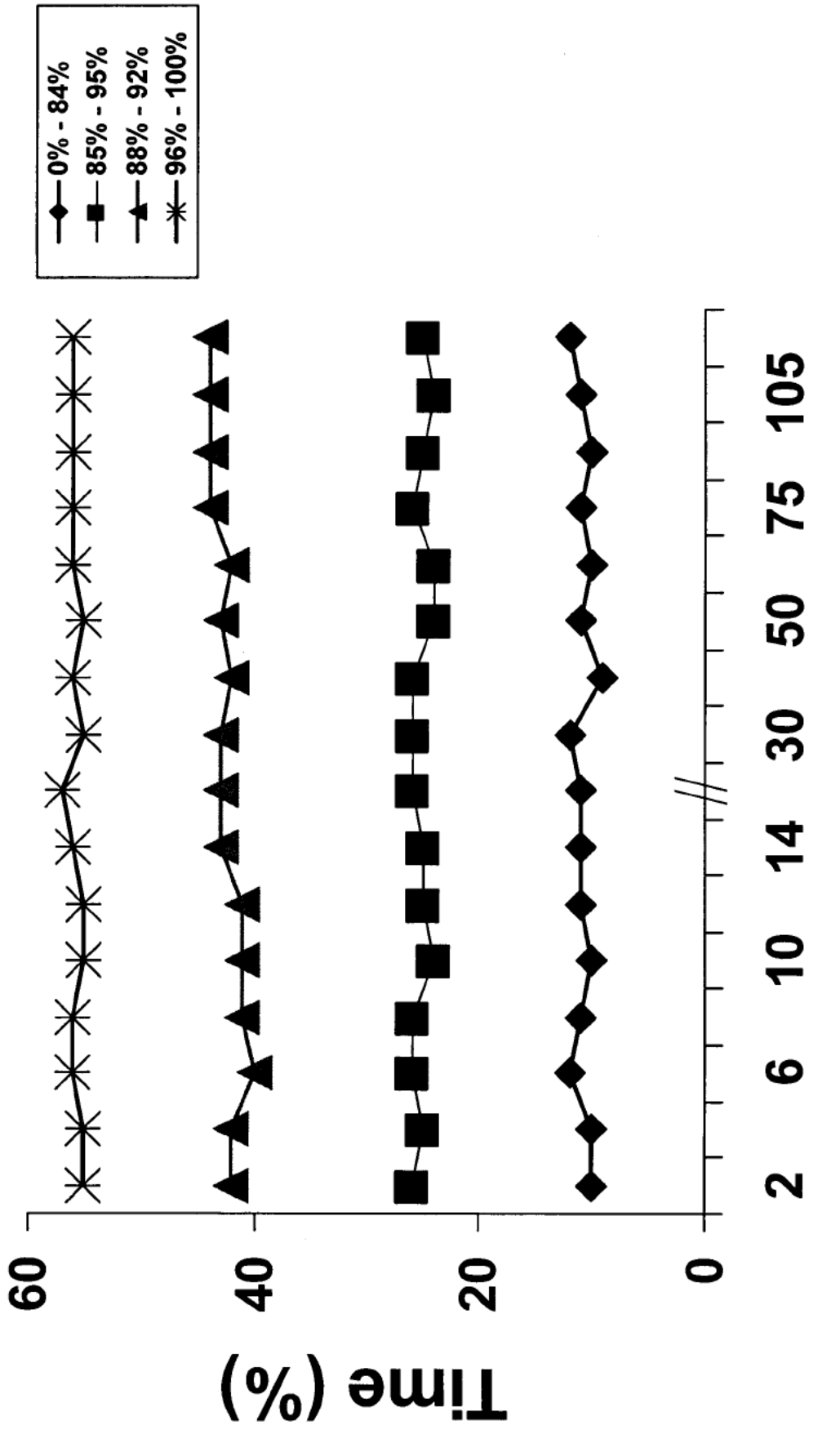
Hi Rose- we had a situation that I wanted to let you know about as it will occasional happen. A mother with PIH was admitted (b) (6) with dates of 24^1 and she was consented for SUPPORT. She went on to deliver, randomization card was pulled prior to delivery and the infant was 395 grams and could not be intubated after 3 attempts. Resuscitation was stopped at 4 ½ minutes. The baby was very immature appearing and wgt was 395 gm. We can complete the SUPP02 and SUPP03 forms BUT this infant is not eligible for the GDB because of a BW of 395 gm. So there will be no network number. I guess this is one of the infrequent problems that we will see when you merge a data base based on BW and a study based on GA. Please advise if there is anything you would like us do to.....NN

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.; Michele Walsh-Sukys; wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: O2 Saturation graphs
Date: Monday, June 27, 2005 9:43:19 AM
Attachments: O2 Sat data - 6-27-05.ppt

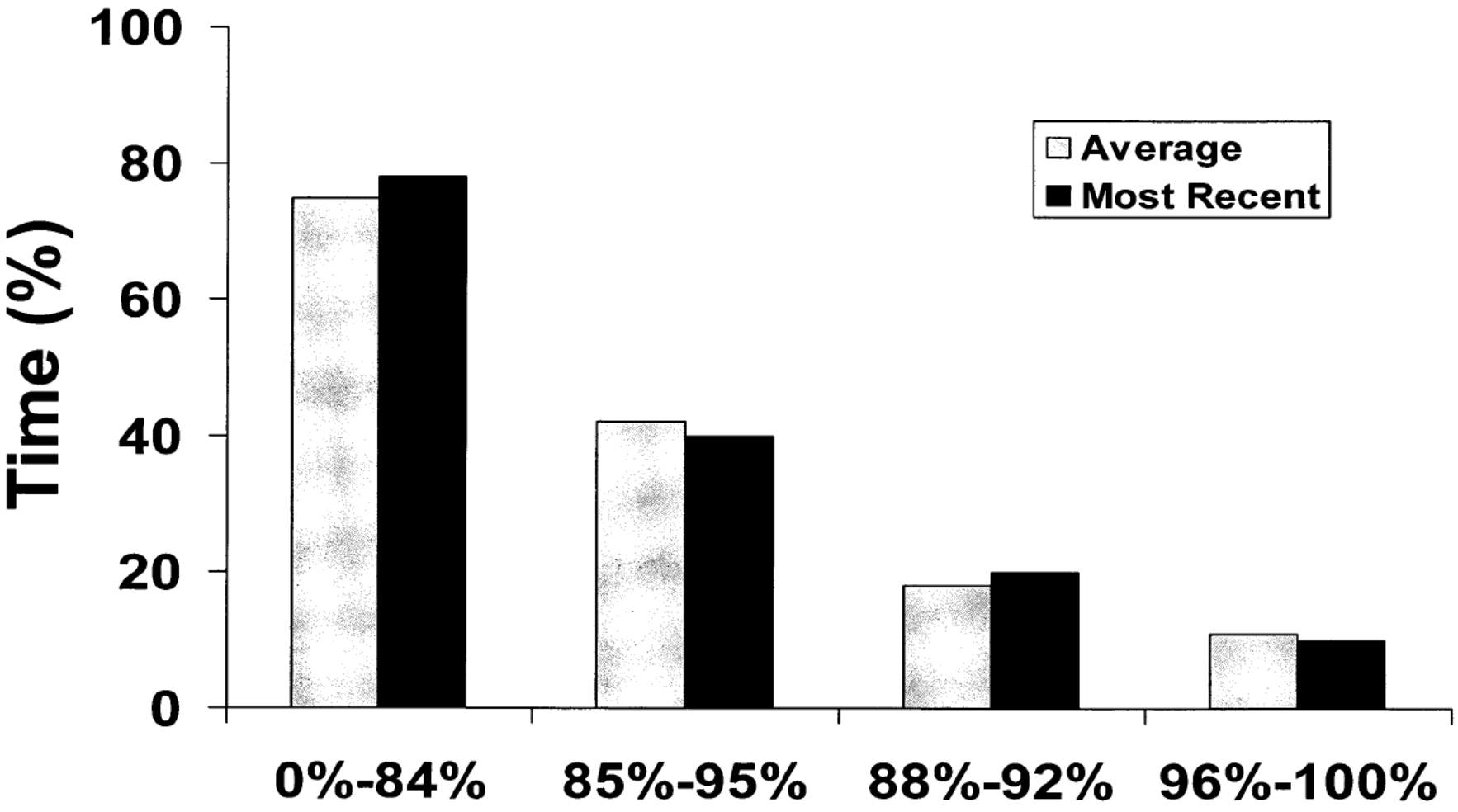
To Support Subcommittee:

Enclosed is attachment that addresses SUPPORT O2 saturation monitoring and compliance. We could discuss this during our next conference call. We discussed briefly at the Steering Committee, options to monitor compliance with the O2 saturation arm of the trial. I have put together several options of ways to analyze the data so we can provide feedback to the DSMB, the Subcommittee, and/or the investigators and colleagues. Please look at the various ways to represent data.

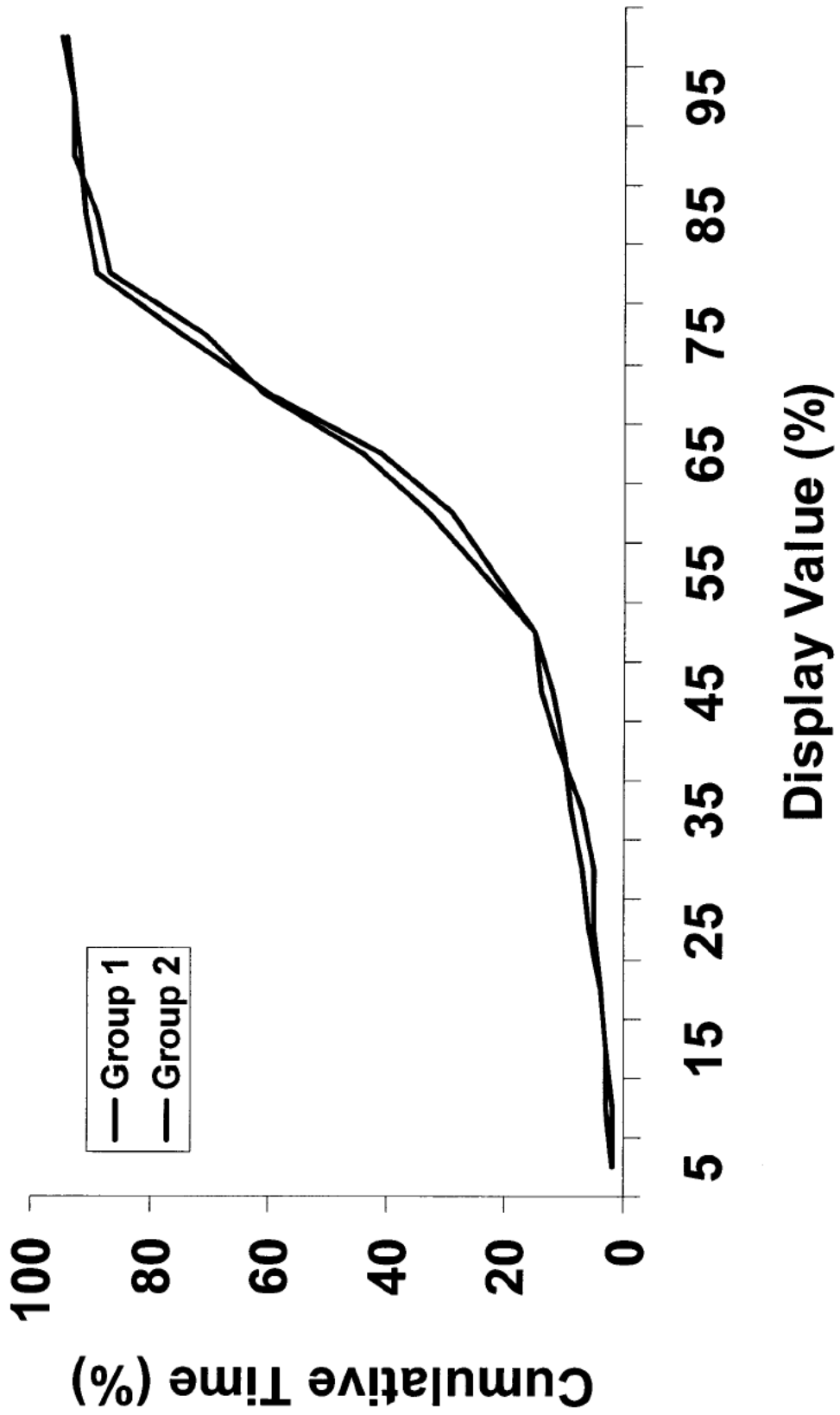
Thanks,
Wally



This figure can also be done grouping a single site vs. the whole trial data.



This figure would be done per site, but can also be done for the whole trial vs. single site.



From:	Neil Finer
To:	"Wally Carlo, M.D."; wrich@ucsd.edu; edward.donovan@chmcc.org; "Duara, Shahnaz"; "Avroy A. Fanaroff, M.D."
Cc:	Higgins, Rosemary (NIH/NICHD) [E]
Subject:	RE: SUPP11 6-22-05 .doc
Date:	Saturday, June 25, 2005 1:35:42 PM

I am OK with whatever the coordinators think is reasonable. We do not have any hypotheses based on FiO2 and if I recall neither BOOST nor STOP ROP reported FiO2 data. I will further clarify
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, June 23, 2005 4:09 AM
To: wrich@ucsd.edu; edward.donovan@chmcc.org; Duara, Shahnaz; Neil Finer; Avroy A. Fanaroff, M.D.
Cc: higginsr@mail.nih.gov
Subject: RE: SUPP11 6-22-05 .doc

Why not record "any O2" (as a Yes or No) as defined in GDB (e.g. not including blow by or for feeds) would be consistent with GDB and much easier to record daily. Remember, this is after the 14 days and it will be hard to analyze FiO2 as it will be administered in many different ways including cannula which results in a highly variable pharyngeal (inspiratory) FiO2.

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, June 22, 2005 6:18 PM
To: edward.donovan@chmcc.org; 'Duara, Shahnaz'; 'Neil Finer'; Wally Carlo, M.D.; 'Avroy A. Fanaroff, M.D.'
Cc: higginsr@mail.nih.gov
Subject: SUPP11 6-22-05 .doc

Dear Support Subcommittee folk:

The coordinators would like the Supp11, which is the data collection form we are using after day 14 for Support, to just record the
highest level of support for the day, regardless of how long it was in use. This would simplify the process, and allow for some cross checking of data for
quality purposes down the road. Do any of you have a problem with using "highest level of support" rather than "highest level >4 hours"? Neil is
basking in the sun in Hawaii, so I have come to you for guidance.

Wade

From: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Pulmonary outcomes secondary study
Date: Friday, June 24, 2005 5:31:49 PM

Rose, thank you.
ron

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

06/24/2005 02:15 PM

To: Ronald N Goldberg <goldb008@mc.duke.edu>
cc:
Subject: RE: Pulmonary outcomes secondary study

Ron
Ricki had sent this back stating that Duke would administer the questionnaires. Melody had brought this up at the follow up investigators meeting at PAS in May as a concern at the Duke site (and many other sites also acknowledge this concern) as a potential problem as some patients may not want to talk to someone that they have not met in person. This is extremely valid and we thank you and your site for the detailed discussion of issues with the follow up program and contacts!

Rose

From: Ronald N Goldberg [mailto:goldb008@mc.duke.edu]
Sent: Friday, June 24, 2005 2:07 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: Pulmonary outcomes secondary study

Rose,
We are interested but will administer the questionnaires here at Duke.
Ron

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD)" [higginsr@mail.nih.gov]
Sent: 06/17/2005 10:07 AM
To: Abbot Laptook (alaptook@WIHRI.org)" <alaptook@WIHRI.org>; Abhik Das

<adas@rti.org>; Brenda Poindexter <bpoindex@iupui.edu>; Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>; Charles Rosenfeld <crosen@mednet.swmed.edu>; Dale Phelps <dale_phelps@urmc.rochester.edu>; Ed Donovan <edward.donovan@cchmc.org>; Ehrenkranz Richard (E-mail)" <richard.ehrenkranz@yale.edu>; Jobe Alan (E-mail)" <Jobea0@chmcc.org>; Lemons Jim (E-mail)" <jlemons@iupui.edu>; Michael O'Shea" <moshea@wfubmc.edu>; Michelle Walsh <mcw3@po.cwru.edu>; Neil Finer <nfiner@ucsd.edu>; Oh William (E-mail)" <william_oh@brown.edu>; Poole Kenneth (E-mail)" <poo@rti.org>; Ronald Goldberg; Shahnaz Duara <sduara@miami.edu>; Shankaran Seetha (E-mail)" <s_shankaran@wayne.edu>; Stevenson David (E-mail)" <dstevenson@stanford.edu>; Stoll Barbara (E-mail)" <barbara_stoll@oz.ped.emory.edu>; Tyson Jon (E-mail)" <Jon.E.Tyson@uth.tmc.edu>; Walid Salhab (Walid Salhab)" <Walid.Salhab@UTsouthwestern.edu>; Anna Dusick (adusick@iupui.edu)" <adusick@iupui.edu>; Betty Vohr ('Betty_Vohr@brown.edu')" <Betty_Vohr@brown.edu>; Charlie Bauer (cbauer@peds.med.miami.edu)" <cbauer@peds.med.miami.edu>; Dee WIlson (b) (6) (b) (6) ; Gary Myers (Gary_myers@URMC.Rochester.edu)" <Gary_myers@urmc.rochester.edu>; Ira Adams-Chapman <ira_adams-chapman@oz.peds.emory.edu>; Jean Steichen (steichjj@email.uc.edu)" <steichjj@email.uc.edu>; Myriam Peralta (mperalta@peds.uab.edu)" <mperalta@peds.uab.edu>; Ricki Goldstein; Robert Dillard <rdillard@wfubmc.edu>; Roy Heyne <Roy.Heyne@UTsouthwestern.edu>; Susan Hintz <srhintz@stanford.edu>; Yvette Johnson (yjohnson@med.wayne.edu)" <yjohnson@med.wayne.edu>; Yvonne Vaucher (Yvonne Vaucher)" <yvaucher@ucsd.edu>

Cc: Hastings, Betty J." <bkh@rti.org>; (kzaterka@rti.org)" <kzaterka@rti.org>; Petrie, Carolyn" <petrie@rti.org>

Subject: Pulmonary outcomes secondary study

Hi
Attached are documents and questionnaires associated with the pulmonary outcomes secondary study to the SUPPORT Trial. Please review the documents and send me a preference by June 27 indicating the following:

1. My site will do the Questionnaires
2. Rochester site to do questionnaires on my study subjects

I am checking on the issues regarding how the consents would be phrased in order that information could pass from your site to the Rochester site.

Thanks in advance for all your help!!
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Risa Demetrio
To: Nancy Peters; wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: bkh@rti.org; Michael O`Shea
Subject: RE: Oximeters for SUPPORT
Date: Thursday, June 23, 2005 7:17:21 PM

Thanks a bunch Nancy.
Risa

-----Original Message-----
From: Nancy Peters [mailto:npeters@wfubmc.edu]
Sent: Thursday, June 23, 2005 12:22 PM
To: wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD); Risa Demetrio
Cc: bkh@rti.org; Michael O`Shea
Subject: RE: Oximeters for SUPPORT

Thanks. Our Masimo Rep told us otherwise!!!! --- that is why we went to the trouble to label them.

Nancy

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, June 23, 2005 3:01 PM
To: 'Higgins, Rosemary (NIH/NICHD)'; Nancy Peters; risa.demetrio@sharp.com
Cc: bkh@rti.org; Michael O`Shea
Subject: RE: Oximeters for SUPPORT

Nancy,
Thanks a bunch. I think you methods are excellent, but just so you know, there is no reason to match the base and the front. All of the data is stored in the oximeter.
The docking station
has no information in it, so in a pinch any base which was shipped to you for this trial could be used.
Thanks again.
wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 23, 2005 11:48 AM
To: 'npeters@wfubmc.edu'; 'risa.demetrio@sharp.com'
Cc: 'bkh@rti.org'; 'wrich@ucsd.edu'; 'moshea@wfubmc.edu'
Subject: Re: Oximeters for SUPPORT

Nancy and Mike
Thanks so much!!
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Nancy Peters <npeters@wfubmc.edu>

To: Risa Demetrio <risa.demetrio@sharp.com>
CC: Hastings, Betty J. <bkh@rti.org>; wrich@ucsd.edu <wrich@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; Michael O`Shea <moshea@wfubmc.edu>
Sent: Thu Jun 23 14:47:09 2005
Subject: Oximeters for SUPPORT

Risa,

I am shipping to you by overnight Fed Ex one blue and one orange oximeter, as requested by Wade. They are:

Docking Station 059903 and orange oximeter 311004, and

Docking Station 059698 and blue oximeter 310914

You will note that we have labeled ours as pairs (this oximeter #### with docking station ######) so that if the oximeter is taken out of the docking station then it is a double check that it is put back in the correct unit for that baby (for download purposes). In addition, I have put plastic pockets on the top of our docking stations which holds a yellow index card.
We plan to put the name of the child (addressograph or label) on the plain side (so hopefully the oximeter moves with the child from bed to bed or from unit to unit) and use the lined side to help track downloads (so any study staff could go by a bed and be aware of the download status).

Let me know if you need any additional units. My pager is (336) 806(b) (6)
I will usually pay attention to pages until 11pm ---and don't promise that I will hear my pager if it goes off during the night (a little "ibuprofen related" hearing loss issue). Home telephone number is (336) 785(b) (6)

Nancy Peters

From: Michael O`Shea
To: Higgins, Rosemary (NIH/NICHD) [E]; Nancy Peters; risa.demetrio@sharp.com
Cc: bkh@rti.org; wrich@ucsd.edu
Subject: RE: Oximeters for SUPPORT
Date: Thursday, June 23, 2005 2:53:17 PM

As usual, Nancy did all the hard work :-)

Mike

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 23, 2005 2:48 PM
To: Nancy Peters; 'risa.demetrio@sharp.com'
Cc: 'bkh@rti.org'; 'wrich@ucsd.edu'; Michael O`Shea
Subject: Re: Oximeters for SUPPORT

Nancy and Mike
Thanks so much!!
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Nancy Peters <npeters@wfubmc.edu>
To: Risa Demetrio <risa.demetrio@sharp.com>
CC: Hastings, Betty J. <bkh@rti.org>; wrich@ucsd.edu <wrich@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; Michael O`Shea <moshea@wfubmc.edu>
Sent: Thu Jun 23 14:47:09 2005
Subject: Oximeters for SUPPORT

Risa,

I am shipping to you by overnight Fed Ex one blue and one orange oximeter, as requested by Wade. They are:

Docking Station 059903 and orange oximeter 311004, and

Docking Station 059698 and blue oximeter 310914

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We plan to put the name of the child (addressograph or label) on the plain side (so hopefully the oximeter moves with the child from bed to bed or from unit to unit) and use the lined side to help track downloads (so any study staff could go by a bed and be aware of the download status).

Let me know if you need any additional units. My pager is (336)

806(b) (6)
I will usually pay attention to pages until 11pm ---and don't promise that I will hear my pager if it goes off during the night (a little "ibuprofen related" hearing loss issue). Home telephone number is (336) 785(b) (6)

Nancy Peters

From:	Petrie, Carolyn
To:	Petrie, Carolyn; Neil Finer; Duara, Shahnaz; Edward Donovan; wcarlo@peds.uab.edu; mcw3@po.cwru.edu; Poole, W. Kenneth; Das, Abhik; reverett@med.miami.edu
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Hastings, Betty J.; Zaterka-Baxter, Kristin; wrich@ucsd.edu
Subject:	RE: SUPPORT secondary Protocol- antenatal consent
Date:	Thursday, June 23, 2005 10:53:44 AM
Attachments:	Draft form 04 26 05.doc

In addition to the protocol, here is the antenatal secondary data form.

-----Original Message-----
From: Petrie, Carolyn
Sent: Thursday, June 23, 2005 10:32 AM
To: 'Neil Finer'; 'Duara, Shahnaz'; 'Edward Donovan'; 'wcarlo@peds.uab.edu'; 'mcw3@po.cwru.edu'; Poole, W. Kenneth; Das, Abhik; 'reverett@med.miami.edu'
Cc: 'higginsr@mail.nih.gov'; Hastings, Betty J.; Zaterka-Baxter, Kristin; 'Wade Rich (wrich@ucsd.edu)'; Petrie, Carolyn
Subject: SUPPORT secondary Protocol- antenatal consent

To the Support Subcommittee:

Attached is the SUPPORT secondary on antenatal consent for your review and discussion for the next conference call.

Carolyn

Center: ___ Study No.: _ _ _ Network No. (if assigned): _ _ _ _ _ Site: ___ Mother's initials: _ _ . _ _

Complete on all mothers screened for the SUPPORT trial

Was the mother approached for consent Y N

If YES, what was the GA by best OB estimate at the first contact for consent _____ . __
Weeks Days

If NO; Why not
1= Active labor, 2= Insufficient time, 3= Weeknight,
4= Weekend, 5= Holiday, 6= Neonatal consult not done yet
7= Not notified /aware of admission ____

If consent was attempted:
Total # of attempts: ____
No: of attempts by the Research nurse ____

Did you get OB permission to approach for antenatal consent? Y N

Was a neonatal consult performed for this subject? Y N
If YES:
Was consent discussed during the consultation? Y N
Was consent obtained during consultation? Y N

If a consult was obtained prior to consent was it required by the IRB?
Y N

Did this patient deliver within the study window? Y N

Was this mother approached for in any other antenatal studies ? Y N UNK

If yes: a) Maternal studies b) Neonatal studies? Y N

Was consent obtained for this study?

Estimate the time it took to obtain a decision regarding consent:
1= <30 mins, 2= 30 mins to < 1H, 3= 1H to < 2H,
4= 2H to < 4H, 5= ≥ 4H _____

From: Higgins, Rosemary (NIH/NICHD)
To: Barbara Stoll
Subject: FW: SUPPORT secondary Protocol- antenatal consent
Date: Thursday, June 23, 2005 10:47:00 AM
Attachments: Antenatal Consent Protocol0622.doc

-----Original Message-----
From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Thursday, June 23, 2005 10:32 AM
To: Neil Finer; Duara, Shahnaz; Edward Donovan; wcarlo@peds.uab.edu; mcw3@po.cwru.edu; Poole, W. Kenneth; Das, Abhik; reverett@med.miami.edu
Cc: Higgins, Rosemary (NIH/NICHD); Hastings, Betty J.; Zaterka-Baxter, Kristin; wrich@ucsd.edu; Petrie, Carolyn
Subject: SUPPORT secondary Protocol- antenatal consent

To the Support Subcommittee:

Attached is the SUPPORT secondary on antenatal consent for your review and discussion for the next conference call.

Carolyn

Title of Project: Antenatal Screening and Consent in a Research Network Model

Principal Investigator: Wade Rich, BS, RRT-NPS, UCSD Medical Center

Co-Investigators: Kathy Auten, Duke University, Ellen Hale, Emory University, Angelita Hensman, Brown University, Nancy Newman, Case Western Reserve University, Nancy Peters, Wake Forest University Medical Center

Facilities: Neonatal Research Network

Duration of Study: **2 years**

Specific Aims: Objectives:

This proposed secondary study is designed to evaluate the screening and consent process to determine the factors that contribute to obtaining antenatal consent for a complex 2x2 factorial trial in an experienced multi-center cooperative research network. Our objectives are:

1) To determine the average number of attempts to present a study to a prospective parent and the average length of time it takes to obtain an answer regarding participation for all centers and between centers.
2) To determine how many mothers must be approached for consent to yield one enrolled subject.
3) To determine the amount of personnel time it takes to yield one enrolled subject.
4) To determine reasons for failure to obtain consent.
5) To determine reasons for failure to enroll consented newborns.
6) To make recommendations regarding budgeting and antenatal recruitment practices for future neonatal studies.

Background and Significance:

With advances in neonatal and perinatal medicine, it has become common for women to be approached in the antenatal period to discuss obstetrical and/or neonatal research studies. Studies which involve treatment in the delivery room have historically been either consented antenatally or have functioned under a waiver of consent as established in the Code of Federal Regulations (45 CFR 46.116[d], 21CFR50.24[a]2(iii)).[1-3] Because institutional review boards and federal regulations are becoming more strict regarding the use of a waiver, most multi-center trials have chosen to obtain consent. In complex multi-factorial trials significant time and multiple explanations may be necessary to ensure that the information is presented appropriately. Funding for clinical trials sponsored by federal agencies or industry sponsors is most often based on a model of capitation in which a site is paid based on the number of subjects enrolled. However, this model does not account for time spent by research staff to explain the study design and research procedure to all eligible potential subjects, many of whom are never enrolled. Since consent rates can vary widely depending upon the nature and complexity of a study, it is important that study sponsors support the effort required, whether or not they result in consent. Early enrollment in the NICHD Neonatal Research Network SUPPORT trial has shown that antenatal screening and consent are labor intensive, and that actual patient enrollment numbers may be significantly lower than screening and consent rates.

The DRCPAP trial was conducted to determine the feasibility of recruiting adequate patients antenatally as well as randomizing them to CPAP in the delivery

room.. Of 214 consented families, approximately 50% were enrolled. No data on screening were collected for this trial.[1] The most common reason for failure to enroll was that the pregnancy extended beyond the study window.

Progress Report/Preliminary Studies:

NICHD neonatal research coordinators perceive antenatal screening as time consuming relative to enrollment rates. An informal survey of coordinators from 13 Network centers shows that the median length of time it takes to meet and discuss a study with a parent antenatally and obtain an answer regarding participation is 2 hours (range 30 minutes to 4 hours.)

Population: Coordinators of the Neonatal Research Network sites who are participating in the SUPPORT trial.

Inclusion criteria:

___Coordinators of the Neonatal Research Network sites.

Exclusion criteria:

Centers not participating in the Support trial.
Coordinators who have not signed an informed consent.

Design and Methods:

This is a prospective cohort study of the antenatal consenting practices of research personnel in a multi-center neonatal research network. Using a one page data collection form, research staff will gather information about the number of eligible women who are approached for consent while hospitalized compared to the number of eligible, hospitalized women who are not approached, and the reasons why they were not approached. They will also collect information about the number of attempts it takes research personnel to contact an eligible, hospitalized woman to discuss the study and obtain an answer regarding whether she wishes to participate, and about which type of researcher (physician, nurse practitioner, or research nurse) seeks consent. Finally, information will be collected regarding whether or not they agree to participate in the study, whether they are approached antenatally for other studies, and, among those who agree to participate, the number that deliver within the window of eligibility. Data will be collected on the first fifty patients screened at each of the 16 NICHD NRN centers. Data forms will be keyed into the NRN computer and transmitted by modem to the data collection center at RTI.

Procedure:

Research coordinators will gather information on every mother who arrives on the labor ward and for whom there is reasonable belief that she will deliver in the study window.

Data Collection and Analysis: Data will be collected daily using data collection form Supp 01a which will be uploaded to the data collection center weekly.

Human Subjects: All infants entered eligible for enrollment in the SUPPORT trial will be approached for this trial. Individual centers may either modify their current protocol or write a stand alone for this secondary trial.

Informed Consent: Study subjects will be the coordinators who gather the data for the SUPPORT trial, all of whom have signed a document agreeing to participate.

Therapeutic Alternatives: N/A

Potential Risks: This is a minimal risk trial, as only data involving the consent process will be obtained. There is a small risk of loss of confidentiality, but this is managed by de-identifying all subject data and using an independent data management organization which receives no PHI from the sites.

Risk/Benefit Ratio: The knowledge gained in this trial will help researchers better understand the process of antenatal consent in a high risk population

Expense to Subject: N/A

Payment for Participation: N/A

Bibliography:

1. Finer N, Carlo W, Duara S, etal. Delivery room continuous positive airway pressure/positive end-expiratory pressure in extremely low birth weight infants: a feasibility trial. PEDIATR 2004; 114:651-657.

2. Saugstad OD, Rootwelt T, Aalen O, et al. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the resair 2 study. Pediatrics 1998; 102:1-7. Abstract.

3. Wiswell T, Gannon C, Jacob J, Goldsmith L, et al. Delivery Room Management of the APparently Vigorous Meconium-Stained Neonate: Results of the Multicenter, International Collaborative Trial. Pediatrics 2000; 105:1-7.

Budget - No cost will be involved in this trial.

From: Higgins, Rosemary (NIH/NICHD)
To: Hastings, Betty J.; Petrie, Carolyn; kzaterka@rti.org
Subject: FW: Protocol
Date: Thursday, June 23, 2005 10:26:00 AM
Attachments: Antenatal Consent Protocol0622.doc

Hi
Here is the protocol from the coordinators. Carolyn - can you send to the SUPPORT subcommittee? I spoke to Wade this AM and the SUPP 11 form is almost ironed out, so the coordinators (Newman, Ball, Hale, Peters, Auten and Henseman) do not need to be on the call. Let me know if there are concerns
Thanks
Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, June 22, 2005 6:32 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Protocol

Rose,
I am attaching the Antenatal Support protocol. You mentioned at the meeting you would help me arrange it so that we could use the coords. as the research subjects. Here is what I came up with. I don't like it. I would appreciate your suggestions.
Wade

Wade Rich, BS,RRT-NPS
Clinical Research Coordinator
Division of Neonatology
UCSD Medical Center
200 W Arbor Dr
San Diego, CA 92103-8774
619-543-5375
pgr 290-5230

Title of Project: Antenatal Screening and Consent in a Research Network Model

Principal Investigator: Wade Rich, BS, RRT-NPS, UCSD Medical Center

Co-Investigators: Kathy Auten, Duke University, Ellen Hale, Emory University, Angelita Hensman, Brown University, Nancy Newman, Case Western Reserve University, Nancy Peters, Wake Forest University Medical Center

Facilities: Neonatal Research Network

Duration of Study: **2 years**

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This proposed secondary study is designed to evaluate the screening and consent process to determine the factors that contribute to obtaining antenatal consent for a complex 2x2 factorial trial in an experienced multi-center cooperative research network. Our objectives are:

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room.. Of 214 consented families, approximately 50% were enrolled. No data on screening were collected for this trial.[1] The most common reason for failure to enroll was that the pregnancy extended beyond the study window.

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Informed Consent: Study subjects will be the coordinators who gather the data for the SUPPORT trial, all of whom have signed a document agreeing to participate.

Therapeutic Alternatives: N/A

Potential Risks: This is a minimal risk trial, as only data involving the consent process will be obtained. There is a small risk of loss of confidentiality, but this is managed by de-identifying all subject data and using an independent data management organization which receives no PHI from the sites.

Risk/Benefit Ratio: The knowledge gained in this trial will help researchers better understand the process of antenatal consent in a high risk population

Expense to Subject: N/A

Payment for Participation: N/A

Bibliography:

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3. Wiswell T, Gannon C, Jacob J, Goldsmith L, et al. Delivery Room Management of the APparently Vigorous Meconium-Stained Neonate: Results of the Multicenter, International Collaborative Trial. Pediatrics 2000; 105:1-7.

Budget - No cost will be involved in this trial.

From: Wally Carlo, M.D.
To: wrich@ucsd.edu; edward.donovan@chmcc.org; SDuara@med.miami.edu; nfiner@ucsd.edu; AAF2@po.cwru.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPP11 6-22-05 .doc
Date: Thursday, June 23, 2005 9:45:38 AM

Got it. Your proposal seems fine.
Wally
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wade Rich <wrich@ucsd.edu>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; edward.donovan@chmcc.org <edward.donovan@chmcc.org>; 'Duara, Shahnaz' <SDuara@med.miami.edu>; 'Neil Finer' <nfiner@ucsd.edu>; 'Avroy A. Fanaroff, M.D.' <aaf2@po.cwru.edu>
CC: higginsr@mail.nih.gov <higginsr@mail.nih.gov>
Sent: Thu Jun 23 07:47:47 2005
Subject: RE: SUPP11 6-22-05 .doc

Wally,

We had already decided on the FiO2 as a Yes or No question as in GDB . The question is about level of support. Can we also define level of support (IMV, SImV, CPAP, etc.)
as Yes or No.

Wade

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, June 23, 2005 4:09 AM
To: wrich@ucsd.edu; edward.donovan@chmcc.org; Duara, Shahnaz; Neil Finer; Avroy A. Fanaroff, M.D.
Cc: higginsr@mail.nih.gov
Subject: RE: SUPP11 6-22-05 .doc

Why not record "any O2" (as a Yes or No) as defined in GDB (e.g. not including blow by or for feeds) would be consistent with GDB and much easier to record daily. Remember, this is after the 14 days and it will be hard to analyze FiO2 as it will be administered in many different ways including cannula which results in a highly variable pharyngeal (inspiratory) FiO2.

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, June 22, 2005 6:18 PM
To: edward.donovan@chmcc.org; 'Duara, Shahnaz'; 'Neil Finer'; Wally Carlo, M.D.; 'Avroy A. Fanaroff, M.D.'
Cc: higginsr@mail.nih.gov
Subject: SUPP11 6-22-05 .doc

Dear Support Subcommittee folk:

The coordinators would like the Supp11, which is the data collection form we are using after day 14 for Support, to just record the

highest level of support for the day, regardless of how long it was in use. This would simplify the process, and allow for some cross checking of data for quality purposes down the road. Do any of you have a problem with using "highest level of support" rather than "highest level >4 hours"? Neil is basking in the sun in Hawaii, so I have come to you for guidance.

Wade

From: Duara, Shahnaz
To: wrich@ucsd.edu; edward.donovan@chmcc.org; Neil Finer; wcarlo@peds.uab.edu; Avroy A. Fanaroff, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPP11 6-22-05 .doc
Date: Thursday, June 23, 2005 9:31:30 AM

Hi Wade,

We deal with this all the time with resp sheets - do we want transient changes? My feeling is that transient changes are usually not recorded, so I'm OK with "highest level of support" if te coordinators feel that would make things flow better.

Shahnaz

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> **From:** Wade Rich [mailto:wrich@ucsd.edu]
> **Sent:** Wednesday, June 22, 2005 7:18 PM
> **To:** edward.donovan@chmcc.org; Duara, Shahnaz; 'Neil Finer'; wcarlo@peds.uab.edu; 'Avroy A. Fanaroff, M.D.'
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>
> Wade

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Subject: Protocol
Date: Wednesday, June 22, 2005 6:31:44 PM
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619-543-5375
pgr 290-(b) (6)

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Payment for Participation: N/A

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Budget - No cost will be involved in this trial.

From: Hastings, Betty J.
To: Petrie, Carolyn
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT conf call Fri Jul 8, 1pm ET
Date: Wednesday, June 22, 2005 2:53:59 PM

Do you think that Angelita, Nancy and Bethany should be on this call? I didn't know if they will be discussing the Antenatal Consent protocol.

-----Original Message-----
From: Petrie, Carolyn
Sent: Tuesday, June 21, 2005 2:46 PM
To: Petrie, Carolyn; Das, Abhik; Poole, W. Kenneth; 'Duara, Shahnaz'; 'Edward Donovan'; 'wcarlo@peds.uab.edu'; 'mcw3@po.cwru.edu'; 'Higgins, Rosemary (NIH/NICHD)'; 'Wade Rich (wrich@ucsd.edu)'; 'reverett@med.miami.edu'; Hastings, Betty J.; Zaterka-Baxter, Kristin; 'Barbara Stoll'
Cc: 'Neil Finer'; 'hsquibb@ucsd.edu'; [SCRN] Dunbar-Scott, Renee; [SCRN] Tinsley, Mazie
Subject: SUPPORT conf call Fri Jul 8, 1pm ET

The SUPPORT conference call is scheduled for
Friday July 8
1:00-2:00pm ET (10-11am PT)

Agenda

- How to fill out screening logs (eligible versus screening)
- Definition of BPD at 36 weeks – three different definitions currently (Dr. Stoll for GDB)
- Pulmonary outcomes secondary

To join the call:
Dial Tollfree: **866-675-**(b) (6)
Passcode: (b) (6) when prompted)

Leader: Rose Higgins

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 902
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: dstevenson@stanford.edu; mbball@stanford.edu
Subject: SUPPORT pulmonary -
Date: Wednesday, June 22, 2005 9:53:24 AM

Hi Rose,

Re: the pulmonary SUPPORT secondary. We are planning to have the Rochester site administer the questionnaire to our patients. We believe our patients would be just as willing to answer those questions through the Rochester call center, as long as we prepare them that someone will be calling.

Thanks

Susan
--
Susan R. Hintz, M.D.
Assistant Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

From: Richard Ehrenkranz
To: srhintz@stanford.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; monica.konstantino@yale.edu
Subject: MRI SUPPORT secondary
Date: Tuesday, June 21, 2005 1:39:05 PM

Susan:
I know that we briefly discussed this issue at the meeting last week: We have been considering making the performance of a MRI at about 36 weeks PMA as part of our standard routine for ELBW infants. No decision has been made yet. Issues about potential sedation for a "routine" clinical MRI, let alone a research MRI are the most problematic. I hope to be able to resolve this issue soon.
Richard

From: Higgins, Rosemary (NIH/NICHD)
To: Phelps, Dale
Subject: RE: SUPPORT GROWTH SECONDARY
Date: Tuesday, June 21, 2005 12:54:00 PM

Dale
This one is still in the review phase and will cost $$. It will need to come to the steering committee for a vote.
Thanks for your candor!
Rose

-----Original Message-----
From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, June 21, 2005 12:53 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT GROWTH SECONDARY

Rose,
I have concerns about the number of secondaries being added ... I'm afraid too many will lead to interference with the primary study. We're pushing the envelope here.
Dale

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD)
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Phelps, Dale; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: Petrie, Carolyn; Hastings, Betty J.; kzaterka@rti.org
Sent: 6/21/2005 9:24 AM
Subject: SUPPORT GROWTH SECONDARY

Hi,

Dr. Cristina Navarrete (University of Miami) is developing a secondary study to the SUPPORT Trial to look at growth. This was presented briefly at the steering committee meeting. The proposal is under revision with the SUPPORT Trial subcommittee. Cristina is in the process of exploring potential options for supplemental/outside funding for this secondary project. Dr. Finer and I have encouraged her to do so; she will apply to the American Thoracic Society.

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

From: Higgins, Rosemary (NIH/NICHD)
To: ric@itsa.ucsf.edu
Cc: ALAN JOBE; Barbara Stoll
Date: Tuesday, June 21, 2005 12:00:00 PM
Attachments: Protocol outline.doc

Ron
Attached is an outline for protocol submission for the NICHD NRN. It would be very helpful for you and Alan to submit a brief description using this outline as a guide. I understand that you would like to assess the impact of the publication of the TIPP Trial on prophylactic indomethacin use across network centers. The Generic Database subcommittee can then review the proposal and make a recommendation.
Thanks
Rose

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higginsr@mail.nih.gov

Protocol outline

A. Abstract

B. Statement of the Problem

C. Hypothesis

D. Specific Aims

E. Rationale/justification

F. Background / Previous Studies

G. Method/ Procedures

1. Description of study design (masked, randomized etc.)_
2. Definition of study population (with inclusion/exclusion criteria)
3. Description of study intervention
4. Precise definition of primary/secondary outcomes
5. Sample size estimate with some statistical support (including estimate of compliance and consent rates) based upon primary outcome.
6. Available population/compatibility with other ongoing protocols
7. Estimate of projected recruitment time

H, Risks/benefits, with estimate of frequency/severity of risks.

I. Budget estimate

From: Roy Heyne
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: JANET MORGAN
Subject: Re: Pulmonary outcomes secondary study
Date: Tuesday, June 21, 2005 9:33:51 AM

Rose, though Dr. Stevens responded to all the questions in my original 5/27 comments, he did not address a couple of additional comments I sent in a 5/31 e-mail. Though no one else brought up either of these points, they are definitely relevant for us in Dallas, and perhaps for others.

I would also be interested to know what he (or others) think of the additional articles I mentioned in several other post-script e-mails.

In case these points got lost in a barrage of other e-mails, I am copying them below in blue italics. Thanks for passing this on.

Rose, FYI.

>>> Roy Heyne 06/02/05 7:42 AM >>>
just ran across two interesting articles from the UK assessing accuracy of parents' interpretations of children's respiratory symptoms: Cane and McKenzie "Parents interpretations of children's respiratory symptoms on video" Arch Dis Child2001; 84:31-34 and Elphick et. al. "Survey of respiratory sounds in infants" Arch Dis Child 2001; 84:35-39.

>>> Roy Heyne 05/31/05 7:46 AM >>>
Janet just reminded me of two more points, which I did not include in my comments last Friday, though I did raise one at our meeting in D.C.: 1) We need to provide some incentive for participation, since this will involve additional time and trouble on the part of the family; 2) as in the case of the PCV7 study, we need the flexibility to be able to enroll and obtain the baseline questionnaire within 2-4 weeks after discharge (at our first follow-up visit), rather than prior to discharge, which latter is a more challenging time to try to connect with our families).

>>> Roy Heyne 05/27/05 5:41 PM >>>
One other interesting article that addresses the llimited accuracy of reported wheezing was published last year in Arch Dis Child 89:540-543 by Lowe et. al.

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 06/17/05 9:07 AM >>>
Hi

Attached are documents and questionnaires associated with the pulmonary outcomes secondary study to the SUPPORT Trial. Please review the documents and send me a preference by June 27 indicating the following:
1. My site will do the Questionnaires

2. Rochester site to do questionnaires on my study subjects

I am checking on the issues regarding how the consents would be phrased in order that information could pass from your site to the Rochester site.

Thanks in advance for all your help!!
Rose

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higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

From: Higgins, Rosemary (NIH/NICHD)
To: Phelps, Dale
Subject: RE: proteomics review
Date: Monday, June 20, 2005 2:26:00 PM

Dale
One other item that has come up with secondaries is the 'Blood draw" and whether or not this should be a separate or opt-out consent. This came up with the SUPPORT subcommittee on multiple occasions. Separate consent is more work, but separates out the blood drawing issue. Opt out may inhibit overall consent for the main trial. Each study and EACH SITE would need to work this out. I don't think I mentioned it on Friday.
Thanks
Rose

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, June 20, 2005 2:25 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: proteomics review

Thanks you very much.

I think we should provide feedback to Dr. Madan (with other reviews) and see what she says.
Dale

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 20, 2005 2:18 PM
To: Phelps, Dale
Subject: proteomics review

Dale
Attached is the review from an expert in proteomics. Let me know if you would like more outside review.
Thanks
Rose

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From: Rebecca Bara
To: bkh@rti.org
Cc: nxs5@cwru.edu; sshankar@med.wayne.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT oximeters
Date: Monday, June 20, 2005 11:42:20 AM

Hi Betty,

Two SUPPORT study oximeters were shipped to Case Western on Friday. Oximeter serial #'s were: 313542 and 313586, docking station serial #'s: 063756 and 063296.

Take care,
Becky

From: Wade Rich
To: "Das, Abhik"; Higgins, Rosemary (NIH/NICHD) [E]; "Schaefer, Scott E."
Cc: "Hastings, Betty J."; "Neil Finer"
Subject: FW: oximeter data loss patient (b) (6)
Date: Monday, June 20, 2005 10:12:23 AM

Abhik,

Dr. Rasmussen downloaded a few of his studied using TExtract and ProFox, a commercial product. ProFox allows you to see minute by minute data, alarms, etcs.
He reviewed study #43 on your list, and found that all of the data was there. Your analysis showed 69% of the data missing. Perhaps we need to redefine the
gaps. I am available today to help with this issue.
Wade

From: Maynard Rasmussen [mailto:maynardr@cox.net]
Sent: Saturday, June 18, 2005 2:29 PM
To: wrich@ucsd.edu; Neil Finer
Cc: risa.diametrio@sharp.com
Subject: oximeter data loss patient (b) (6)

There is not any significant data loss. This infant was on respiratory support from (b) (6) weaned off of RA nasal cannula 3/14. The 1st download contains all the data from (b) (6) The infant was back on respiratory support 4/20-22 after a herniorraphy, weaned off of nasal cannula by 4/24. Recording #2 goes from 4/20 to 4/27. Hope this helps. Maynard

From: Yvonne Vaucher
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Pulmonary outcomes secondary study
Date: Friday, June 17, 2005 11:26:28 AM

Rose,

We will give the questionnaire at our site. I have not had a chance to review the revised one yet so I may have more questions then. In terms of requesting documentation from the primary care providers, we can send the request, however, we will need more personnel time to follow up those that are not returned since nearly everyone of our patients has a *different* primary care provider/different group. I trust there is adequate funding allotted for this. Thanks.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, June 17, 2005 7:07 AM
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab); Anna Dusick (adusick@iupui.edu); Betty Vohr ('Betty_Vohr@brown.edu'); Charlie Bauer (cbauer@peds.med.miami.edu); Dee WIlson (b) (6)); Gary Myers (Gary_myers@URMC.Rochester.edu); Ira Adams-Chapman; Jean Steichen (steichjj@email.uc.edu); Myriam Peralta (mperalta@peds.uab.edu); Ricki Goldstein (golds005@mc.duke.edu); Robert Dillard; Roy Heyne; Susan Hintz; Yvette Johnson (yjohnson@med.wayne.edu); Yvonne Vaucher (Yvonne Vaucher)
Cc: Hastings, Betty J.; (kzaterka@rti.org); Petrie, Carolyn
Subject: Pulmonary outcomes secondary study

Hi
Attached are documents and questionnaires associated with the pulmonary outcomes secondary study to the SUPPORT Trial. Please review the documents and send me a preference by June 27 indicating the following:

1. My site will do the Questionnaires
2. Rochester site to do questionnaires on my study subjects

I am checking on the issues regarding how the consents would be phrased in order that information could pass from your site to the Rochester site.

Thanks in advance for all your help!!
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From:	Higgins, Rosemary (NIH/NICHD)
To:	Abbot Laptook (alaptook@wihri.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O"Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab); Anna Dusick (adusick@pediatrics.wisc.edu); Betty Vohr (bvohr@wihri.org); cbauer@peds.med.miami.edu; drficmd@aol.com; Gary Myers (gary_myers@URMC.Rochester.edu); Ira Adams-Chapman; Jean Steichen (steichji@uc.edu); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); golds005@mc.duke.edu; Robert Dillard; Roy Heyne; Susan Hintz; Yvette Johnson (yrjohnso@bcm.tmc.edu); Yvonne Vaucher
Cc:	Hastings, Betty J.; (kzaterka@rti.org); Petrie, Carolyn
Subject:	Pulmonary outcomes secondary study
Date:	Friday, June 17, 2005 10:07:00 AM
Attachments:	Appendix B shorter.doc Appendix C shorter.doc Response to Network Follow Up PIs.doc SUPPORT Follow-on Study 10-1 (2).doc Appendix A.doc

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Hi
Attached are documents and questionnaires associated with the pulmonary outcomes secondary study to the SUPPORT Trial. Please review the documents and send me a preference by June 27 indicating the following:

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SUPPORT FOLLOW ON STUDY OF RESPIRATORY OUTCOMES

ADMINISTERED BY TELEPHONE AT 6 AND 12 MONTHS CORRECTED AGE

This interview should be completed by the parent/guardian for:

_____

All questions pertain only to his/her health.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Respiratory Outcome Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Before we begin this interview it would be helpful if you could gather any medications your child has been prescribed or has been taking and have them in front of you. Can you do that now or is there a better time to call you?

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing problems your child may have.

VOLUME OF OUTPATIENT PULMONARY CARE

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

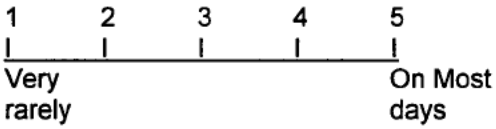
4a. Has his/her chest ever sounded wheezy or whistling?
   3. Yes
   4. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?



e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing ~

g. Has this child's wheezing/whistling occurred as sudden, abrupt onset attacks?
   1. Yes
   2. No

h. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

i. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 21 AND 22

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY (continued)

5a. Has this child ever had a recurrent cough when he/she did not have a cold?

1. Yes
2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6a

b. At what time of the day has this cough usually occurred?
(CIRCLE ALL THAT APPLY)

1. In the morning, shortly after rising
2. Later in the day
3. During the night
4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?

1. Yes
2. No

d. How often has this child been bothered by coughing?

1 2 3 4 5
Very Rarely ... On most days

e. How old was the child when he/she first began to cough?

____ months

f. How old was this child when he/she stopped coughing?

_____ months

OR: check here if child is still coughing: _

g. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?

1. Yes
2. No

h. Has he/she ever seen a doctor about the cough?

1. Yes
2. No

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY (continued)

6a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: ~

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ months

OR: check here if doctor never said he/she had asthma: ~

e. **During the past 6 months**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past 6 months**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 21 AND 22

7. During the past **two weeks**, how often has your child had coughing, wheezing, or shortness of breath *during the day*?

1❑ Never
2❑ Twice a week
3❑ More than two times a week, but not every day
4❑ Everyday, but *not* all the time
5❑ Everyday, all the time

8. During the past **two weeks**, how often has your child had coughing, wheezing, or shortness of breath *during the night*?

1❑ Never
2❑ Once every two weeks or less
3❑ Once a week
4❑ More than 1 night a week
5❑ Frequently/Every night

9. Over the past **two weeks (out of 14 days),** how many **days** did you have to change for daytime or evening plans because of your child's wheezing or coughing: _____# of days

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY (continued)

10a. Has your child ever had bronchiolitis, or any wheezing illness in the past 6 months associated with a viral illness, bronchitis, or pneumonia?

1. Yes
2. No . . . SKIP TO QUESTION 11a

IF **YES** TO QUESTION 10A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. How old was this child when he/she had the last such episode?

_____ months

11a. Has your child had pneumonia in the past 6 months?

1. Yes
2. No . . . SKIP TO QUESTION 12

IF **YES** TO QUESTION 11a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?

1. One episode
2. More than one episode

d. Did your baby receive antibiotics?

1. Yes
2. No

ASCERTAINMENT OF BREAST FEEDING HISTORY

12a. In the past 6 months, did your baby receive mother's breast milk, either at breast, from a bottle or through a tube?

1. Yes
2. No

IF **YES** TO QUESTION 12a:

12b. For how many months was this child breast-fed or received mostly breast milk?

1. Never breastfed / no breast milk
2. Less than 1 month
3. 1-3 months
4. 4-6 months

ASCERTAINMENT OF RESPIRATORY EXPOSURES

13a. Has the **mother** smoked at all since this child was born?

3. Yes
4. No . . . SKIP TO QUESTION 14

IF **YES** TO QUESTION 13a:

b. For how many months did the mother smoke since this child was born? _____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (Note: One Pack Contains 20 Cigarettes)

_____ cigarettes _____ pipes _____cigars _____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?

_____ Never _____ Occasionally _____Frequently

14. Please choose which of the following options best describe the situation regarding smoking in this child's **home**:

$_1$❑ Smoking is allowed in any common room of the home
$_2$❑ Smoking is limited to part of the house where the child rarely goes
$_3$❑ There is no smoking inside at all → Are there any exceptions to this situation?

$_0$❑ No $_1$❑ Yes

Under what circumstances are the exceptions allowed?

_____

15. Please choose which of the following options best describe the situation regarding smoking in your **car**:

$_1$❑ Do not have a car
$_2$❑ Smoking is usually or always allowed
$_3$❑ Smoking is sometimes allowed
$_4$❑ Smoking occurs in the car only when the child is not inside
$_5$❑ There is no smoking inside the car → Are there any exceptions to this situation?

$_0$❑ No $_1$❑ Yes

Under what circumstances are the exceptions allowed?

_____

16. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

16a. How much does this child's primary caregiver smoke?

$_0$❑ Never $_1$❑ Occasionally $_2$❑ Daily

17. How many children other than this child and his/her siblings live in your house? _____

18. Do you have any pets?

1. Yes
2. No

$_1$❑ Dogs #: _____
$_2$❑ Cats #: _____
$_3$❑ Other #: _____

OUTPATIENT RESPIRATORY CARE

PROPHYLAXIS

19. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?
    1. Yes
    2. No

20. Did this child receive a flu shot?
    1. Yes
    2. No

OXYGEN

21a. Is your child on any oxygen therapy (oxygen tank at home)?
    1. Yes
    2. No

IF **YES** TO QUESTION 21a:

*lpm = liters per minute

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

MEDICATIONS

22. Is your child taking any medicines for asthma or wheezing?
    1. Yes
    2. No
    3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as:* ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ QVar ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other _____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

THANK YOU FOR YOUR COOPERATION

SUPPORT FOLLOW ON STUDY
RESPIRATORY OUTCOMES

ADMINISTERED AT 18-22 MONTH FOLLOW UP VISIT

This interview should be completed by the parent/guardian for:

_____

All questions pertain only to his/her health.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Respiratory Outcome Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing concerns your child may have.

VOLUME OF OUTPATIENT PULMONARY CARE

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

4a. Has his/her chest ever sounded wheezy or whistling?
   3. Yes
   4. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?

1	2	3	4	5
Very rarely				On Most days

e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing ~

g. Has this child's wheezing/whistling occurred as sudden, abrupt onset attacks?
   1. Yes
   2. No

h. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

i. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 21 AND 22

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY (continued)

5a. Has this child ever had a recurrent cough when he/she did not have a cold?

1. Yes
2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6a

b. At what time of the day has this cough usually occurred?
(CIRCLE ALL THAT APPLY)

1. In the morning, shortly after rising
2. Later in the day
3. During the night
4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?

1. Yes
2. No

d. How often has this child been bothered by coughing?

1	2	3	4	5
Very Rarely				On most days

e. How old was the child when he/she first began to cough?

____ months

f. How old was this child when he/she stopped coughing?

_____ months

OR: check here if child is still coughing: _

g. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?

1. Yes
2. No

h. Has he/she ever seen a doctor about the cough?

1. Yes
2. No

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY (continued)

6a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: ~

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ months

OR: check here if doctor never said he/she had asthma: ~

e. **During the past 6 months**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past 6 months**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 21 AND 22

7. During the past **two weeks**, how often has your child had coughing, wheezing, or shortness of breath *during the day*?

1❑ Never
2❑ Twice a week
3❑ More than two times a week, but not every day
4❑ Everyday, but *not* all the time
5❑ Everyday, all the time

8. During the past **two weeks**, how often has your child had coughing, wheezing, or shortness of breath *during the night*?

1❑ Never
2❑ Once every two weeks or less
3❑ Once a week
4❑ More than 1 night a week
5❑ Frequently/Every night

9. Over the past **two weeks (out of 14 days),** how many **days** did you have to change for daytime or evening plans because of your child's wheezing or coughing: _____# of days

ASCERTAINMENT OF RESPIRATORY SYMPTOMS, FREQUENCY AND SEVERITY (continued)

10a. Has your child ever had bronchiolitis, or any wheezing illness in the past 6 months associated with a viral illness, bronchitis, or pneumonia?

1. Yes
2. No . . . SKIP TO QUESTION 11a

IF **YES** TO QUESTION 10A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. How old was this child when he/she had the last such episode?

_____ months

11a. Has your child had pneumonia in the past 6 months?

1. Yes
2. No . . . SKIP TO QUESTION 12

IF **YES** TO QUESTION 11a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?

1. One episode
2. More than one episode

d. Did your baby receive antibiotics?

1. Yes
2. No

ASCERTAINMENT OF BREAST FEEDING HISTORY

12a. In the past 6 months, did your baby receive mother's breast milk, either at breast, from a bottle or through a tube?

1. Yes
2. No

IF **YES** TO QUESTION 12a:

12b. For how many months was this child breast-fed or received mostly breast milk?

1. Never breastfed / no breast milk
2. Less than 1 month
3. 1-3 months
4. 4-6 months

ASCERTAINMENT OF RESPIRATORY EXPOSURES

13a. Has the **mother** smoked at all since this child was born?

3. Yes
4. No . . . SKIP TO QUESTION 14

IF **YES** TO QUESTION 13a:

b. For how many months did the mother smoke since this child was born? _____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (Note: One Pack Contains 20 Cigarettes)

_____ cigarettes _____ pipes _____cigars _____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?

_____ Never _____ Occasionally _____Frequently

14. Please choose which of the following options best describe the situation regarding smoking in this child's **home**:

$_1$❑ Smoking is allowed in any common room of the home
$_2$❑ Smoking is limited to part of the house where the child rarely goes
$_3$❑ There is no smoking inside at all → Are there any exceptions to this situation?

$_0$❑ No $_1$❑ Yes

Under what circumstances are the exceptions allowed?

_____

15. Please choose which of the following options best describe the situation regarding smoking in your **car**:

$_1$❑ Do not have a car
$_2$❑ Smoking is usually or always allowed
$_3$❑ Smoking is sometimes allowed
$_4$❑ Smoking occurs in the car only when the child is not inside
$_5$❑ There is no smoking inside the car → Are there any exceptions to this situation?

$_0$❑ No $_1$❑ Yes

Under what circumstances are the exceptions allowed?

_____

16. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

16a. How much does this child's primary caregiver smoke?

$_0$❑ Never $_1$❑ Occasionally $_2$❑ Daily

17. How many children other than this child and his/her siblings live in your house? _____

18. Do you have any pets?

1. Yes
2. No

$_1$❑ Dogs #: _____
$_2$❑ Cats #: _____
$_3$❑ Other #: _____

Appendix C

OUTPATIENT RESPIRATORY CARE

PROPHYLAXIS

19. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?
    1. Yes
    2. No

20. Did this child receive a flu shot?
    1. Yes
    2. No

OXYGEN

21a. Is your child on any oxygen therapy (oxygen tank at home)?
    1. Yes
    2. No

IF **YES** TO QUESTION 21a:

*lpm = liters per minute

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

MEDICATIONS

22. Is your child taking any medicines for asthma or wheezing?
    1. Yes
    2. No
    3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as:* ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	$_1$❑ Everyday $_2$❑ Sometimes $_3$❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	$_1$❑ Everyday $_2$❑ Sometimes $_3$❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ Other_____	$_1$❑ Everyday $_2$❑ Sometimes $_3$❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	$_1$❑ Everyday $_2$❑ Sometimes $_3$❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other_____	$_1$❑ Everyday $_2$❑ Sometimes $_3$❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	$_1$❑ Everyday $_2$❑ Sometimes $_3$❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other _____	$_1$❑ Everyday $_2$❑ Sometimes $_3$❑ Only when Sick

ATOPY HISTORY

23. **During the past year**, for how many days has this child been unable to do his/her usual activities because of illnesses such as chest
(not head) colds, bronchitis, asthma or pneumonia?

_____ days

24. How many head colds (common colds) **per year** does this child usually have?

1. Few (0-3 per year)
2. Some (4-5 per year)
3. Frequent (6-9 per year)
4. Constant (more than 9 per year)

25a. Has your child **ever** had hay fever or any other condition that makes his/her nose runny, stuffy, or itchy **apart** from colds?

1. Yes
2. No . . . SKIP TO QUESTION 26

IF **YES** TO QUESTION 25a:

b. How old was your child when you first noticed this condition?

_____ months

c. How old was this child when he/she stopped having this condition?

_____ months

OR: check here if child still has condition ~

d. When this child has the runny or stuffy nose, does he/she also usually:

Cough?	1. Yes 2. No
Wheeze?	1. Yes 2. No
Have shortness of breath?	1. Yes 2. No

26. Has this child **ever** had allergies which cause nose, eye or lung problems?

1. Yes
2. No

27. Has a doctor **ever** told you that this child had sinus trouble?

1. Yes
2. No

28a. Has this child **ever** been allergic to any food?

1. Yes
2. No

b. Has he/she **ever** been allergic to any medicine?

1. Yes
2. No

29a. Has this child **ever** had eczema (allergic skin rash)?

1. Yes
2. No . . . SKIP TO QUESTION 30a

IF **YES** TO QUESTION 29A:

b. Has a doctor told you this child had eczema?

1. Yes
2. No

c. At what age did the eczema begin?

_____ months

d. How old was this child when he/she last had eczema?

_____ months

OR: check here if child still has eczema ~

30a. Was this child breast fed or did he/she receive mostly breast milk?

1. Yes
2. No . . . SKIP TO QUESTION 31

IF **YES** TO QUESTION 30a:

b. For how many months was this child breast fed?

1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

31. At what age was formula introduced?

1. Never
2. less than 1 month
3. 1-3 months
4. 4-6 months
5. more than 6 months

32. At what age was cow's milk (nonformula) started?

1. Never
2. Less than 1 month
3. 1-3 months
4. 4-6 months
5. 7-9 months
6. 9-11 months
7. 12 or more months

33. At what age did he/she begin to receive table foods?

1. less than 1 month
2. 1-3 months
3. 4-6 months
4. 7-9 months
5. more than 9 months

THANK YOU FOR YOUR COOPERATION

SUPPORT Trial Pulmonary Outcomes Follow On Study

Response to Follow Up PI Comments

Timothy P. Stevens, MD, MPH

6/15/05

REVIEWER 1

1. The majority of our families are low income and more than 45% are exclusively or primarily Spanish speaking. The questionnaire needs to be administered in person by a fluent, culturally informed, Spanish speaker. In San Diego we will need a Spanish speaker familiar with the local, Mexican Spanish.

Response: Upon finalization of the questionnaires, Spanish language versions will be created. The Cornell Translation Service, a University based professional translation service, will be contracted to perform the translation. We agree that administration of the questionnaire by a native speaker of the local Spanish dialect would be important. For further discussion of Spanish translation, see response to Reviewer 3, comment 1. Further consideration of regionally specific Spanish versions (i.e. Mexican vs. Puerto Rican) of the questionnaires can be considered if local centers identify such a need.

2. Many of our families are very difficult to contact via telephone even after multiple attempts. Many will not even speak to strangers over the phone. Even with willing, English speaking parents, we have had considerable difficulty doing the Network follow-up questionnaires over the phone. The questionnaire needs to be done in person at by a member of our staff at the time of the clinic visit.

Response: Each center has different patient populations and administration of the questionnaire will have to be individualized to meet the needs of these different populations.

3. The person administering the questionnaire needs to have clinical **pediatric**, not neonatal, experience in order to obtain accurate information from the families.

Response: We agree that pediatric clinical expertise will be useful in administration of the questionnaire. For centers choosing Rochester to administer the questionnaire to their patients, we will provide a trained individual to undertake each interview. For centers choosing to administer the questionnaire locally, each center will be free to choose their primary interviewer who has necessary skills. In addition, a training program will be organized to train interviewers in an effort to help standardize the interview.

4. We routinely schedule children at 6 and 12 months, but these are not designated as "Network" visits and the time allotted is much shorter. The length and complexity of the questionnaire would have a significant impact upon the time and personnel needed for those visits.

Response: We recognize the incremental time and effort needed to administer the questionnaire and anticipate incremental funding to meet these requirements.

5. What funding will be provided? Administration of the questionnaire as written will be very time consuming for families whose children have any history of respiratory

problems. The 18 month follow-up visit is already quite long as is with all the required testing and questionnaires. We cannot keep adding more tasks, questionnaires, even when the goal is worthwhile, without additional funding to cover the time and personnel to accomplish them. As it is now, the NIH reimbursement does not cover the actual cost of tracking, 6 and 12 month visits, etc. (The extra $150 for RCT patients will help cover what we already do.)

Response: Please see response to question 4. The final budget is being prepared.

6. As written the questionnaire is much too long and detailed to be administered three times. Can it be substantially "pruned" and tailored to each visit?

Response: We have "pruned" and tailored the questionnaire for the 6 and 12 month interviews, focusing on the main outcomes of wheezing, cough, pulmonary related health care visits and medication use as well as major confounders such as tobacco use. The 18-22 month questionnaire will include questions on broader pulmonary symptoms such as croup as well as more broadly considering other confounders such as atopy.

7. We do not have access to medical records to confirm parent perception/answers. Our patients have multiple pediatric care providers, almost none of which are at UCSD. Most children are followed at various neighborhood clinics or at the local Children's Hospital for their specialty care. Data collected will therefore be based entirely on parental recall. Neither do we have the time/personnel to review medical records even if they were available.

Response: We plan to offer a $25 honorarium to the office-based providers to review their records, extract the pulmonary visit data and forward the results to us. Although chart review may underestimate the need for health services and provide incomplete validation in some cases, especially cases in which primary care is not centralized, health service utilization is a blinded outcome measure of a randomized controlled trial and therefore bias favoring one study arm over another should not occur.

Permission for release of this data will be obtained at the time of consent. Each center will mail the form to the primary care physician. Data entry of completed forms will be returned to the local center for data entry.

8. Parents may recall roughly how many times and where their child was seen/hospitalized. They will not be able to recall, and we cannot confirm, the actual dates.

Response: We agree that the actual dates will be difficult to recall and difficult to precisely confirm. However, the purpose of recording the date or month of the visit is to prevent "double reporting" of the same visit/hospitalization as might occur if the interviewer cannot review the prior visit history prior to a subsequent interview.

9. Specific questions about the questionnaire itself:

If there is interest in breastfeeding history, the questionnaire needs to be adapted to our ELBW population. For instance, we need to ask "'Did your child ever receive **any** breastmilk since for many this will have occurred by gavage/bottle and often only during their stay in the NICU. We might ask specifically if they received MBM in the NICU and after discharge. Also, they may have never been

actually "breastfed" because some mothers still feed only expressed MBM by bottle after discharge. Whatever the questions, the feeding history, particularly with respect to breastfeeding and addition of formula, needs to be asked at 6 and 12 months to minimize recall bias.

Response: The reviewer raises a very good point. In the revised questionnaire, we have included language that better reflects the various feeding routes commonly used for premature infants (question 12). We agree that questioning the family at 6 month intervals likely reduces recall bias. The questionnaires are developed to be administered at 6 month intervals and collect interval history. The questionnaires have been edited to make this clearer.

Can parents ascertain if children less than 6 months old are "awakened by wheeze or shortness of breath?" Most are awakening to feed, especially in the first few months.

Response: Although present in the Tucson questionnaire, we agree that this question is difficult to answer in infants. This question has been replaced by questions 7 – 9 (1;2). Taken from the NHLBI Wheezing Severity Survey, these three questions will allow more accurate and standardized assessment of symptom severity and frequency as well as capture the diurnal pattern of wheezing.

Question 6 e "OR check here is the child is still coughing" belongs under 6 f.

Response: Thank you for this correction.

Qvar needs to be added to inhaled steroids. Is Tilade still on the market?

Response: Thank you, this change has been made. Similar changes may need to be made in the future as the wheezing pharmacopoeia evolves.

REVIEWER 2

I think the Pulmonary secondary for SUPPORT will potentially answer some very important questions - but I have the following concerns, some of which we briefly discussed at the Follow-up meeting on May 16, 2005:

1) Spanish interpretation - I agree with Roy that this could be a very difficult problem. At Stanford, we too have quite a few Spanish-speaking only patients. The questionnaire is quite complicated, and precise interpretation of the questions will be essential. However, I suspect that this problem can be resolved.

Response: Please see response to Reviewer 1, comment 1.

2) Validity and reliability of the instrument: in person vs. by telephone - Has a formal validation study been performed with respect to the method of administering this instrument (in person vs. by telephone)? It appears that the 6- and 12- month data collection will be performed by telephone and the 18-month data will be collected at the follow-up visit (in person). This may not even be a problem if the instrument has already been validated for telephone and in-person reliability in a previous study.

Response: The Tucson Children's Respiratory Study administered the questionnaires both in person and by phone, depending on patient availability. The investigators did not undertake a formal validation of phone vs. face-to-face administration of the questionnaire. Anecdotally, based on phone conversation with the study coordinator, investigators did not observe a difference in quality of responses between phone and questionnaires administered in person.

3) Differences for individual subjects and across centers in terms of how the instrument is administered - It seemed like the question of who was going to call families (and perhaps even if the data collection was going to happen in person or by telephone) was going to be left up to each center. So, it's possible that there will be great variation in how the questions are to be asked - and thus sources of error and bias could be quite variable across subjects and centers.
Response: For centers choosing Rochester to administer the questionnaire to their patients, we will provide a trained individual to perform each interview. For centers choosing to administer the questionnaire themselves, a training program is planned that will help standardize administration.

4) Time for data collection - this seems like a very long questionnaire, and could impact on follow-up staff time quite a bit. Will there be additional compensation for centers - particularly if the questionnaire will be administered at 6 and 12 months by the center follow-up staff rather than the Rochester site?
Response: We recognize the incremental time and effort commitment needed to administer the questionnaire and provide incremental funding to meet these requirements.

Again, I think the study asks some extremely important questions - I am sure these issues above will be able to be addressed.

REVIEWER 3

SUPPORT Trial Pulmonary Outcomes Follow On Study

Comments by R. Heyne, M.D. Dallas 5/27/05

As I indicated at the recent Follow-up PI meeting in Washington, I think a study to follow pulmonary outcomes beyond the nursery is definitely indicated in this population; however, I have a number of concerns regarding the study design, both with regards to the outcome measures chosen, the method of ascertainment, and thus the interpretation and validity of the outcome data the study will produce.

1) Definition of Outcomes: As pointed out in the Background and Methods sections of the protocol, a variety of parent questionnaires have been used in prospective cohort studies to identify and quantify, and/or otherwise characterize, lower respiratory symptoms and/or disease in the first 2-3 years of life. However, the extent of published validation of various survey questions in cited references 48-

54 is less clear. Koopman et. al. (reference 43 in the protocol) reviewed all these cited studies, along with several more, and still raised some of the same questions/concerns I have regarding the accuracy of various reported symptoms.

a. This is especially true in the case of wheezing, which is the most commonly studied, yet probably most problematic, reported symptom.
    i. Members of non-wheezing families do not necessarily recognize a wheeze properly, and upper respiratory noises are difficult to differentiate from wheeze. "Whistling" is not much more helpful.
    ii. Even when families bring the child in to the office for possible "asthma" symptoms, it may not be as simple as it seems to help them precisely recognize/differentiate wheezing. It may take experience over time with variations on the theme, depending on how "classical" the child's presentation is, before they develop a more sensitive/specific ability.
    iii. Many languages do not have a precise (specific) equivalent for wheezing; and there can be interesting dialect/colloquial variants.
    iv. Many of our Spanish families report "ronco," which is almost as non-specific as "gripe." And not all are aware of other terms, such as "jadeo" or "chiflido."
    v. It is not clear that any of the reported surveys have been validated in different languages, Spanish or otherwise.
    vi. Trying to define/differentiate wheezing for the first time over the phone can be challenging and time-consuming, even for someone who knows the family/child.

Response to comment 1a: Thank you for your thoughtful consideration of the challenges of administering questionnaires in two languages. The problem of multiple Spanish words meaning "wheezing" and the potential for Spanish speaking people of different ethnicities to use different words for the same symptom was not appreciated by us in the first proposal. After considering this problem, we propose using an audioclip of wheezing that can be played over the phone or in person. Accompanying the audio, the interviewer would explain that wheezing is an expiratory, whistling-type breathing noise. We do not have validation that this approach is superior to simple questioning, but feel that this approach is the best way to bridge the language gap that exists between English and Spanish and among Spanish speaking populations using different dialects or colloqualisms. An example of an audioclip of wheezing can be provided upon request.

We agree that wheezing symptoms are often only recognized over time. This is one reason why we feel collecting 6 month interval histories is essential if we are to measure the true prevalence of wheezing and the time course of the symptom.

b. Even something as common, and seemingly simple, as a "cold" means different things to different people, and may include everything from a bout of allergic rhinitis to non-specific rhinorhea to a full-blown viral upper respiratory infection with fever, etc.

Response: We agree that the phrase "cold" can mean different things to different people. To avoid ambiguity, the interviewers will define the common cold as follows: "The common cold generally involves a runny nose, nasal congestion, and sneezing. Other symptoms include sore throat, cough, and headache."
However, questions 4 and 5 refer to wheezing or cough that is NOT associated with a "cold". The absence of rhinitis, rhinorrhea or URI is more easily assessed than is the etiology of a "cold". Of course, by excluding wheezing associated with a cold, we may underestimate the true prevalence of non allergic or infectious wheezing. However, because wheezing is a blinded outcome measure from a randomized controlled trial, bias favoring one study arm over another should not occur.

c. Cough is less equivocal per se, but precisely characterizing its nature and frequency is more of a challenge. Moreover, though we all recognize "cough variant asthma," the prognostic value/significance of cough in infancy for later asthma is less clear.

Response: The reviewer raises an important question, is cough a better measure of airway dysfunction in infants than is wheezing. Whether individual symptoms (wheezing or chronic cough, alone) or a combination of these symptoms (wheezing and/or chronic cough, together) best quantifies pulmonary morbidity following premature birth is controversial. Many studies have used wheezing alone as a primary outcome measuring pulmonary morbidity in formerly premature infants (3-6). In 1996, Greenough reported pulmonary morbidity using a combined outcome of either wheezing or chronic cough in infants born < 35 weeks' gestation. She found that greater pulmonary morbidity was associated with longer durations of supplemental oxygen and mechanical ventilation (7;8). Later, in a follow-up study of infants enrolled in the randomized trial entitled, The United Kingdom Oscillator Study (UKOS), Greenough found that frequent wheezing episodes but not chronic cough were associated with neonatal respiratory events (9;10). To address this issue most conservatively, wheezing and chronic cough will be measured as separate outcomes. Secondary analyses will evaluate these symptoms as combined outcomes (wheezing or chronic cough). In addition to parental report of wheezing and chronic cough, respiratory medication use and medical chart review will be conducted to support the parental history. For both wheezing and chronic cough, medication use and respiratory symptoms will be interpreted together, because effective medications may reduce the frequency and severity of symptoms.

We will use wheezing (and cough) as outcome measures of a NICU study intervention rather than as predictors of subsequent asthma or atopy.

d. Asking about a history of physician-diagnosed "asthma" may also over or under state the case, for several reasons:
    i. Physicians may variously apply the term asthma to one or more bouts of "reactive airway disease."
    ii. As Brooks et. al. (protocol reference #14) point out, "physicians may be more or less likely to attribute wheezing in a LBW child to 'asthma' depending on their belief that wheezing is expected in children born prematurely."

iii. In the case of ELBW infants, outpatient physicians are more likely to carry on with a diagnosis of BPD or CLD of prematurity, rather than introduce the new term of "asthma" (or RAD), which can have other connotations to parents.
iv. Without some further information concerning quality and quantity of symptoms, direction and magnitude of possible bias is hard to accurately assess.

Response: We agree that symptom severity is an important aspect of the wheezing outcome. In the revised, more focused questionnaire, three questions from the NHLBI Wheezing Severity Survey have been added to allow more accurate and standardized assessment of symptom severity and frequency of wheezing (questions 7-9). In addition to parental report of wheezing and chronic cough, respiratory medication use and medical chart review will be conducted to support the parental history.

As the reviewer points out, we cannot exclude the possibility of minor degrees of over or underestimation of pulmonary morbidity in some patients using our research design. In administering the questionnaires, every effort will be made to accurately measure the occurrence of pulmonary symptoms and health care and medication use, thus establishing the true incidence of pulmonary morbidity in the study population as a whole. Most importantly, however, because pulmonary morbidity is a blinded outcome measure from a randomized controlled trial, bias favoring one study arm over another should not occur.

e. Possible solutions would include one or more of the following:
i. Some further definition/explanation of terms for families at the outset of the study, in oral and/or written form;

Response: We agree as outlined in response to Reviewer 3, comment 1. Verbal or written explanations could easily be developed to orient the respondent to the exact definition of the symptom or to the intent of the question.

ii. Some reminder/reinforcement during the phone interview, which would lengthen an already lengthy interview;

Response: As mentioned in the previous response, a reminder or reinforcement could be included. The incremental time to administer the questionnaire should be offset by the time saved in administering the revised more focused questionnaire.

iii. Some further validation through chart audit, which would be much more time consuming and much less feasible where primary care is not centralized.

Response: Please see response to reviewer 1, comment 7 above. We agree that chart review may underestimate the need for health services and provide incomplete validation in some cases, especially those cases in which primary care is not centralized. However, because health service utilization is a blinded outcome measure from a randomized controlled trial, bias favoring one study arm over another should not occur.

2) Ascertainment of Outcomes

a. For children who have had more than an isolated bout or two of one or more of the symptoms in the questionnaire, which necessitates answering another 4-9 questions for each leading positive symptom, the questionnaire can turn into a very long phone interview.

Response: The revised questionnaire is more focused and shorter, hence limiting the duration of the interview.

b. Precision of recall of number of office visits, never mind dates of such, is going to be progressively limited, the greater the number of visits, even for periods as short as 6 months.
c. Even for more dramatic events such as ER and hospitalization, precision of date recall is going to be limited.
d. Koopman et. al. have suggested that recall bias may influence results.

Response to comments b-d: We agree that the actual dates will be difficult to recall and difficult to confirm. However, the purpose of asking dates or months is so the interview can review this data prior to a subsequent interview and ask the family if a visit recalled during the second or third interview was already reported on a prior interview. These dates do not need to be exact for the purposes of clarifying the family's responses and avoiding "double reporting" of the same visit/hospitalization.

e. Though a centralized approach to phone interviews may have the benefits listed, it would not succeed with our families for the following reasons:
    i. A significant percentage of our families are not U.S. citizens, and would be very wary of anyone they have not met calling them, even if this was explained ahead of time.
    ii. Central staff do not have the same rapport or familiarity with the families that local study staff have.
    iii. Additional tracking/contacts by central staff would likely be more counterproductive than synergistic.

Response: Please see response to Reviewer 1, comments 1-3. In addition, for those centers choosing Rochester to administer the questionnaires, we propose that the local center track the patients and relay that information to Rochester for the purpose of contacting the parents for the telephone interview. Hence, there would be no duplication of efforts.

3) Additional Questionnaire Issues: Appendix B&C
    a. Questions 4a-j
        i. Question b., as a., may refer to more than one episode of wheezing, some of which may not have been associated with colds, whereas others were. (As noted above, "colds" is not defined.)
        ii. Question g. does not define "attacks"

Response: The description, "sudden, abrupt onset" attacks has been added. As mentioned above, the interviewers will define the common cold as follows, "The common cold generally involves a runny nose, nasal congestion, and sneezing. Other symptoms include sore throat, cough, and headache."

b. Questions 6a-j
    i. Question b sounds as if it is referring to a single or "prototypical" episode, whereas both 6 (a) and b could well refer to multiple different types of episodes.

Response: We agree that the wording of this question could inadvertently be interpreted to mean a single cough. The question is meant to describe a recurring cough. The word "recurring" has been added to clarify the intent of this question.

c. Questions 7a-f
    i. Questions e-f ask about the "past year" whereas the interval should only be 6 months for the 6, 12, and 18 month surveys.

Response: Thank you for this correction.

d. Questions 8a-d
    i. Question a. appears to lump "any wheezing illness....not due to asthma" along with bronchiolitis. Not sure where BPD/CLD or bronchitis fit in to this equation.

Response: Our hypothesis is that wheezing will be reduced (incidence, frequency and severity) among infants treated with a lower targeted oxygen saturation range. As part of this, we wish to capture wheezing like illnesses/episodes, whether infectious or non-infectious in origin. The point of this question was to capture infection associated episodes of wheezing. To better measure this, the question has be edited to read, "10a. Has your child ever had bronchiolitis, or any wheezing illness in the past 6 months associated with a viral illness, bronchitis, or pneumonia?"

e. Questions 11a-d
    i. Without knowing basis for diagnosis of pneumonia (exam +/- CXR +/- WBC), viral vs. bacterial, not sure what we can make of this history. Might at least want to ask about antibiotics and hospitalization.

Response: Thank you for this suggestion. A question regarding treatment with antibiotics has been added to this section.

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NICHD SUPPORT Trial Follow-on Study of Outpatient Pulmonary Outcomes

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A. ABSTRACT

Statement of Problem Premature infants have a greater risk for wheezing and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor for later wheezing, the etiology of recurrent wheezing in formerly premature infants is not known.

Hypotheses The goal of the clinical project detailed here is to understand better the antecedents of recurrent wheezing among preterm infants during early childhood by evaluating the effect of treatment with different levels of targeted oxygen saturation in the immediate neonatal period. **The overarching hypothesis is that premature infants exposed to supplemental oxygen suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater symptomatic airway dysfunction when challenged with subsequent environmental or infectious exposures.**

Hypothesis #1- Relative to infants managed with a higher SpO2 range, infants who are managed with a lower targeted SpO2 range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' corrected age (CA) whether they develop CLD or not.

Hypothesis #2- Relative to infants managed with prophylactic surfactant and conventional ventilation, infants who are managed with the early use of CPAP and a permissive ventilator strategy will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' CA whether they develop CLD or not.

Design

Longitudinal follow-up of infants enrolled in the SUPPORT Trial to determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the prevalence of recurrent wheezing and volume of outpatient pulmonary care in the first 18 months' CA.

Definition of outcomes:

A) Parental Report of Wheezing
B) Physician Diagnosed Wheezing.
C) Volume of Outpatient Pulmonary Care including number of pulmonary medications, office and emergency room visits and re-hospitalizations for respiratory illnesses.

Ascertainment of outcomes:

Outcomes will be measured at 4 time points in the first 18-22 months' CA as follows:

1. NICU discharge -baseline interview at to obtain family and environmental history
2. Six months' CA - telephone interview to ascertain prevalence of wheezing and obtain interval history of need for pulmonary care.
3. Twelve months' CA - telephone interview as at 6 months'
4. 18-22 months' CA- Prior to NICHD follow-up clinic visit, a telephone interview to ascertain prevalence of wheezing and obtain interval history of need for pulmonary care will be administered and primary care physician contact information collected for outpatient office chart review.
5. Outpatient chart review- data extraction from patient outpatient medical record.

Anticipated Results

We anticipate that, for infants who develop CLD and those who do not, treatment with a lower vs. higher targeted oxygen saturation range will result in less frequent episodes of wheezing and less need for outpatient pulmonary care in the first 18-22 months' CA.

Benefits and Risks

The proposed SUPPORT Follow-on Pulmonary Outcome Study will directly measure symptomatic airway dysfunction and outpatient pulmonary morbidity in infants treated with either a higher vs. lower targeted oxygen saturation. These data will provide important insight into the effect of different levels of supplemental oxygen exposure on airway growth and development in formerly premature infants. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the neurodevelopmental follow up visit. We anticipate no risk to the patient of this observational follow-on study.

B. STATEMENT OF THE PROBLEM

Premature infants have a greater risk for wheezing and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor for later symptomatic airway dysfunction, the etiology of recurrent wheezing in formerly premature infants is not known.

C. HYPOTHESES

The overarching hypothesis is that premature infants exposed to supplemental oxygen and, to a lesser extent, mechanical ventilation, in the neonatal period suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction and respiratory symptoms when challenged with subsequent environmental or infectious exposures.

Specific Hypotheses:

Hypothesis #1- We hypothesize that relative to infants managed with a higher SpO2 range, infants managed with a lower SpO2 range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care at 18-22 months' CA.

Hypothesis #2- We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

Hypothesis #3- We hypothesize that **among infants with CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

Hypothesis #4- We hypothesize that **among infants without CLD**, infants managed with early use of CPAP and permissive ventilator strategy relative to infants managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

D. SPECIFIC AIMS

The goal of this project is to understand better the etiology of recurrent wheezing among formerly premature infants during early childhood by examining the interaction of oxygen exposure (targeted SpO2 range), surfactant therapy and early nasal CPAP in the newborn period.

SA#1 - Measure the effect of lower vs. higher targeted SpO2 on the prevalence of recurrent wheezing and volume of outpatient pulmonary care among infants born $24^{0/7}$ - $27^{6/7}$ weeks' gestation during the first 18-22 months' CA.

SA#2 - Measure the effect of early CPAP and permissive ventilator strategy compared with prophylactic surfactant and traditional ventilator strategy on the prevalence of recurrent wheezing and volume of outpatient pulmonary care among infants born 24-27 weeks' gestation during the first 18-22 months' CA.

SA#3 – Among infants who develop CLD, determine whether CLD is milder in infants managed with low compared with high targeted SpO2 by measuring recurrent wheezing and volume of outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

SA#4 – Among infants who do not develop CLD, determine whether pulmonary outcome is better for infants managed with a low compared with high targeted SpO2 range by measuring the prevalence of recurrent wheezing and need for outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory

strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

E. RATIONALE/JUSTIFICATION

Although synergy in producing airway injury may exist between oxygen toxicity and mechanical forces applied to the lung, animal and human data suggest that exposure to high concentrations of supplemental oxygen alone is sufficient to cause airway narrowing and greater reactivity to subsequent challenges. Understanding the relative contributions of oxygen toxicity and mechanical forces on airway growth and development may facilitate development of targeted therapies for preventing or reducing symptomatic airway dysfunction in premature infants.

Why measure recurrent wheezing and outpatient pulmonary care as an outcome from a clinical NICU interventional trial?

1) Important information will be available on the effect of oxidant gas exposure on airway development and later symptomatic airway dysfunction. Exposure to oxidant gas has been causally linked with later wheezing. Existing data on the relationship between supplemental oxygen therapy and wheezing come from longitudinal cohort studies, a design that suffers from intrinsic limitations that make controlling for potential confounders of respiratory outcome difficult. By randomizing infants to higher vs. lower target saturation ranges, and thereby presumably higher or lower concentrations of inspired oxygen, *the SUPPORT Trial creates a unique, and perhaps the only, opportunity to evaluate the effect of different levels of supplemental oxygen on subsequent symptomatic airway dysfunction and need for outpatient pulmonary care after NICU discharge.*

2) Using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care can be directly quantified, allowing assessment of whether infants both with and without CLD have improved pulmonary health as a result of the study intervention.

3) The incidence of CLD, defined as an oxygen requirement at 36 weeks' PMA, is an incomplete measure of pulmonary outcome in formerly premature infants during early infancy. CLD as defined above reflects alveolar gas diffusion and NICU oxygen needs. However, outpatient pulmonary morbidity for formerly premature infants is often airway related, involving wheezing either as a primary symptom such as bronchiolitis or as a complicating symptom of lower respiratory tract infection such as pneumonia. The studies proposed here will directly measure the effect of a randomized NICU-based clinical intervention on symptomatic airway dysfunction and outpatient pulmonary morbidity.

4) The risk of a negative trial is reduced. Because the diagnosis of CLD does not completely predict need for outpatient pulmonary care, clinically significant improvements in pulmonary morbidity may occur with minimal or no change in the incidence of CLD. This result has occurred in other interventional trials in which no difference in CLD were observed (12).

5) At present, there is no standard way to measure symptomatic airway dysfunction in premature infants in NICHD pulmonary intervention trials. There is need for a better measure to assess clinical pulmonary outcome to recognize and promote therapies that reduce need for outpatient care of former extremely premature infants.

6) By measuring outpatient pulmonary outcomes, the cost-effectiveness of the SUPPORT study interventions can be assessed. It is reasonable to expect that the SUPPORT Trial interventions will improve outpatient pulmonary outcomes for infants who ultimately develop CLD as well as those who do not. This proposed follow-on study collects the primary data necessary to quantify the cost-effectiveness of this therapy.

F. BACKGROUND / PREVIOUS STUDIES

Recurrent Wheezing In Preterm Infants is a Significant Public Health Problem

Outpatient pulmonary morbidity, especially recurrent wheezing and need for outpatient pulmonary care, is an understudied but clinically important outcome measure for former premature infants with and without CLD. Infants born weighing < 1500 grams (very low birth weight, VLBW) and especially infants born weighing < 1000 grams are at increased risk for small airway narrowing, airway hyperreactivity, wheezing, and nighttime cough (1-11). Up to 30-40% of formerly extremely premature infants have episodes of wheezing after NICU discharge with many requiring bronchodilators and frequent health care visits. Up to 40-50% of premature infants require re-hospitalization, mostly for treatment of respiratory illnesses (9;12;13). In analysis of cross sectional data from the National Maternal Infant Health Survey and 1991 Longitudinal Follow up Survey, the prevalence of asthma-like recurrent wheezing varied markedly with birth weight. Infants with normal birth weight (NBW, > 2500 grams) had a 6.7% prevalence of asthma compared to 10.9% of low birth weight infants (LBW, 1500-2499 grams) and 21.9% for VLBW (14). Mean per capital asthma related costs have been estimated to be 5 times greater for VLBW compared with NBW infants. The net effect is that VLBW infants, who comprise 2% of asthma patients, consume up to 7% of asthma-related therapy costs (14).

Animal Studies

Animal studies suggest that exposure of the premature lung to hyperoxia (without concomitant mechanical ventilation) for relatively brief periods is sufficient to cause airway remodeling and smooth muscle changes that predispose toward airway narrowing and hyperreactivity to subsequent environmental challenges (15-18). In a rhesus monkey model of asthma, Schlegle et al. exposed infant monkeys to repeated cycles of inhaled House Dust Mite Allergen (HDMA), ozone or filtered air. While repeated exposure to either ozone or HDMA had mild effects, exposure to cycles of ozone followed by HDMA resulted in asthma like changes with significant increases in serum IgE, serum histamine, peripheral eosinophilia and greater airway reactivity. Using supplemental oxygen rather than the stronger oxidant ozone, Schulman et al. found that exposure of newborn guinea pigs to 70% oxygen for 96 hours resulted in airway hyperreactivity at 2 and 9 days after the cessation of oxygen. In cell models, intracellular glutathione buffers airway cells against oxidant injury during hyperoxia (19;20). Although the critical period for lung development is comparatively brief in laboratory animals compared with human infants, the duration of hyperoxic exposure (and risk of oxygen toxicity) for treatment of neonatal lung disease may extend for much longer periods in premature infants known to be deficient in anti-oxidant systems such as intracellular glutathione.

Premature Infants <u>With CLD</u> Are At Greatest Risk For Recurrent Wheezing

Among premature infants, infants with bronchopulmonary dysplasia (BPD) are at highest risk for poor pulmonary outcome after NICU discharge. Infants with CLD have small airway compromise with decreased forced expiratory flow velocities, airway hyperreactivity, and increased functional residual volume suggesting airway obstruction (2;5;9;21-24). In a pulmonary follow up of infants with HMD or BPD, De Klein et al. found infants with BPD had reduced FEV1 at baseline while infants with RDS but not BPD had significant improvements in FEV1 following bronchodilator therapy. In this study, a history of recurrent wheezing predicted abnormal pulmonary function (25). In a recent study of infants with CLD, Robin et al. found that 50% of infants with CLD had symptoms of recurrent wheezing and 35% showed significant airway responsiveness to bronchodilators, evidenced by a 24% increase in forced expiratory flow velocity at 75% of expired forced vital capacity (FEF_{75}). This study demonstrated the relationship between recurrent wheezing as a clinical symptom and the physiologic measurement of airway obstruction. Infants with CLD and a history of recurrent wheezing showed greater expiratory flow limitation, hyperinflation, and airway responsiveness to albuterol compared to those without a history of recurrent wheezing (24).

Premature Infants Without CLD Have Significant Airway Dysfunction

Among VLBW infants who do not develop CLD, several studies of pulmonary outcome have found an association between neonatal oxygen exposure and increased prevalence of expiratory flow dysfunction and airway hyperreactivity (4;11;26-29). Some authors attribute reductions in airway function to intrinsically small airways as a consequence of poor intrauterine growth rather than superimposed airway injury or reactivity from neonatal respiratory disease (1;30). However, because small airways alone do not fully explain findings of airway hyperreactivity, other mechanisms of small airway dysfunction are necessary to explain respiratory symptoms.

Several pulmonary outcome studies have reported significant increases (2-fold or more) in airway obstruction among VLBW infants without CLD following exposure to as little as an FIO2 of 0.4 for 5 days (3;4;8;26). Not all studies have had similar results suggesting variability in effect or susceptibility of babies to oxygen exposure (31;32). In 1982, Coates et al. described increased small airway resistance at 10 year follow up of mildly premature infants (mean gestational age 31 weeks and birth weight 2000 grams) treated with a high oxygen (O2) regimen and those exposed to a low O2 regimen for the treatment of respiratory distress syndrome (RDS). Mechanical ventilation was not used in either group. Pulmonary function tests were performed on survivors receiving either the low or high supplemental oxygen regimen ten years after their initial illness. Infants treated with high levels of supplemental oxygen alone (no mechanical ventilation) had decrements in airway function similar to decrements in function reported for a historical cohort of RDS survivors treated with ventilation and high levels of supplemental oxygen. From these data, the authors concluded that neonatal exposure to high oxygen concentrations in the absence of mechanical ventilation is capable of causing long-term change in small airways (28). These studies suggest that use of lower supplemental oxygen concentration may improve respiratory health of infants who do not develop CLD.

Premature Infants Without CLD Have Increased Risk of Recurrent Wheezing and Need for Outpatient Pulmonary Care.

For VLBW infants without CLD, the prevalence of parental or physician reported wheezing is increased compared with term infants, with estimates of the prevalence of wheezing ranging from 10-38% (4;8). Prevalence of wheezing requiring medications is greater compared with term infants. VLBW infants have a 2-4-fold increase in respiratory related re-hospitalization rates compared with term infants (4;8;33-35). Although most studies have found the risk of recurrent wheezing remains elevated throughout childhood, an Australian longitudinal follow-up cohort of VLBW infants found the prevalence of wheezing remained elevated for 2 years then returned to baseline (32;36).

Prevalence of Symptomatic Airway Dysfunction in Formerly Preterm Infants During the Surfactant Era Remains High

With the advent of surfactant therapy, survival for small infants increased dramatically and the incidence of CLD changed minimally (37-40). Classic BPD evolved into the new CLD characterized by reduced alveolarization and more variable airway changes (41). Pulmonary follow up studies during the surfactant era showed reduced pulmonary morbidity in surfactant treated patients. Typical of these studies, Sell et al. found the incidence of asthma was significantly lower in infants given synthetic surfactant compared with those given air placebo. Pelkonen et al. performed PFT measurements on 40 children aged 7-12 years who were born before 30 weeks of gestation with an immature surfactant system, and were randomized to one of three treatment groups: prophylactic surfactant, rescue surfactant and placebo (air). Spirometric parameters of preterm born children were compared with those of 20 children born at term. Bronchial obstruction was found in 53% of the prophylactically treated group, in 36% of the rescue group, in 67% of the placebo group, and in 0% of the control group (42). A recent report suggests that the introduction of surfactant therapy markedly altered the pulmonary outcome of premature infants. Published in 2001, the Newborn Lung Function Project Group reported results of a prospective 12-year follow-up of VLBW infants following the introduction of surfactant therapy. Among infants with CLD, wheezing symptoms decreased from 50 to 16% from the period before compared with the period after surfactant therapy became available. However, among infants without CLD the prevalence of wheezing increased from 14% to 38% with the introduction of surfactant. These data suggest that surfactant therapy has an effect on outpatient respiratory health and underscores the need to

consider outpatient pulmonary outcomes in evaluating therapeutic strategies that potentially decrease surfactant replacement therapy.

CLD is an Incomplete Predictor of Outpatient Pulmonary Morbidity

Several authors have looked to respiratory symptoms and need for outpatient pulmonary care as outcome measures for neonatal lung disease (9;10;12;24). In 1988, from a retrospective chart review of 605 premature infants < 1500 grams, Shennan et al. found that the presence of BPD (oxygen requirement at 36 weeks PMA) had a 63% positive predictive value and a 90% negative predictive value for abnormal pulmonary outcome in the first 2 years of age. However, this study from before the era of exogenous surfactant therapy defined abnormal pulmonary outcome as death, oxygen requirement at 40 weeks PMA, 2 or more respiratory related hospital admissions, wheezing requiring drug therapy or persistent wheezing resulting in growth failure, handicap or hypotonia at 1 year of age. Such restrictive criteria for abnormal pulmonary outcome are likely to underestimate the burden of recurrent wheezing on former premature infants and their families. Several recent interventional studies show that CLD is an incomplete predictor of clinical wheezing and need for outpatient pulmonary care and suggest that differences in oxygen exposure or oxidant stress may affect pulmonary outcome without affecting the incidence of CLD.

Interventional Trials That Did Not Reduce CLD But Did Reduce Outpatient Pulmonary Morbidity.

Recent data in preterm infants treated with human recombinant superoxide dismutase (SOD) found that anti-oxidant therapy did not reduce the incidence of CLD. However, among infants < 27 weeks gestation SOD therapy resulted in significant reductions in the first year after NICU discharge in the number of emergency room visits and number of re-hospitalizations for respiratory problems and reductions in the need for bronchodilators suggesting a reduced prevalence of wheezing in patients treated with SOD (12). In a randomized, multi-center trial from Helsinki, N acetyl cysteine did not reduce the incidence of CLD. Outpatient pulmonary outcome of these patients has not been reported.

Treatment of Premature Infants With Higher Targeted Oxygen Saturations Is Associated with Poorer Pulmonary Outcome

In the STOP-ROP Study, infants exposed to higher levels of oxygen to achieve a targeted saturation of 96-99% compared with 89-94% had greater risk of adverse pulmonary events including pneumonia, chronic lung disease exacerbations and need for diuretics, oxygen and hospitalization at 3 months'' corrected age. *Although all infants in this study had CLD at enrollment, different targeted oxygen saturation were associated with large differences in pulmonary morbidity.* Adverse pulmonary outcomes occurred with differences in FIO2 of as little as 10% for patients treated with ventilation, CPAP or hood (36% $\pm$ 14% vs. 46% $\pm$ 20%, respectively for low vs. high saturation range) and 5% for infants treated with nasal cannula, (26% $\pm$ 6% vs. 31% $\pm$ 11%, respectively for low vs. high saturation range) (44). In a similar study, The Benefits of Oxygen Saturation Targeting (BOOST) Trial randomized infants < 30 weeks' gestation to higher (95-98%) or lower (91-94%) saturations ranges beginning at 32 weeks' PMA to determine whether infants managed with higher targeted saturation range showed better growth and neurodevelopment. As in the STOP-ROP study, need for oxygen therapy was prolonged. Trends towards an increased risk of pulmonary death and fewer outpatient office visits (median 27.5 vs. 31.3, $p < .11$) were seen in the lower targeted oxygen saturation group (13).

G. METHOD/ PROCEDURES

NICHD SUPPORT Trial Follow-on Study of Pulmonary Outcomes

G.1 Description of study design

This study will add an 18-22 month longitudinal, prospective follow-on study of surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial.

G.2 Definition of study population

Infants with gestational age of $24^{0/7}$-$27^{6/7}$ weeks' gestation by best obstetrical estimate.

Inclusion criteria:

- Full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Parents/legal guardians have provided consent for enrollment
- No known major congenital malformations
- Survival to hospital discharge

Exclusion Criteria

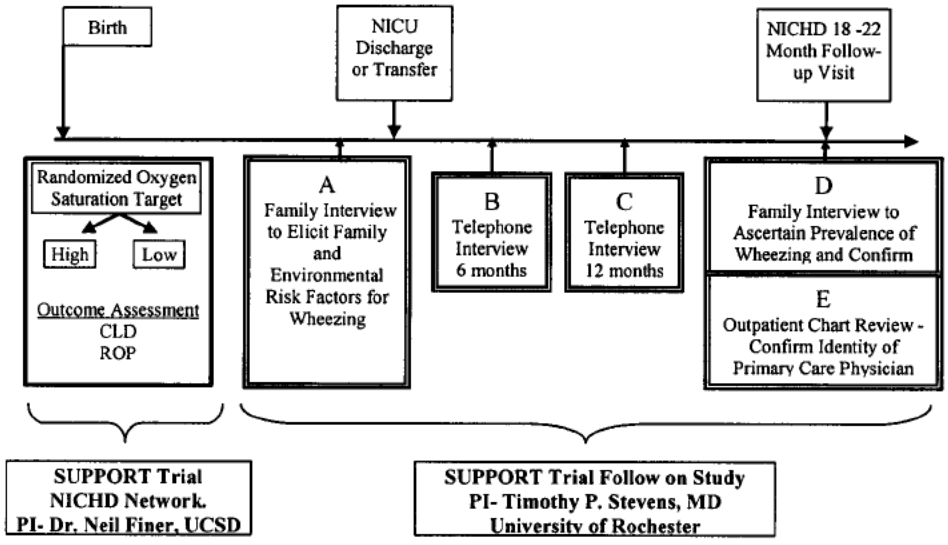
- Transport to the center after delivery
- Parents/legal guardians refuse consent
- Research apparatus/study personnel are not available.
- Gestational age $< 24^{0/7}$ or $\geq 28^{0/7}$ weeks' gestation

G.3 Description of study intervention

Before delivery, infants will be randomized to subsequent management with high vs. low target oxygen saturation according to the SUPPORT Protocol. The SUPPORT Follow-on Study proposed here begins just prior to NICU discharge (Figure 1).

SUPPORT Trial Follow-on Study

Figure 1. **Infants $24^{0/7}$-$27^{6/7}$ Weeks' Gestation**



"A" will be administered at NICHD Network Centers

"B-E" will be conducted long distance by University of Rochester research staff.

Fig 1, A. Parent (Guardian) Interview to Elicit Family and Environmental Risk Factors for Wheezing The family interview will be administered at each participating Network Center by site study nurses prior to NICU discharge or transfer. The questions are based on intake questions used by the Tucson Respiratory Study and are designed to elicit family history of asthma, atopy, and home environment and to identify likely care givers (Questionnaire in Appendix G). Consent for release of medical information will be obtained to facilitate contacting physician offices to obtain office data.

Fig 1, B. Telephone Interview at 6 months' CA – respiratory interval history

Fig 1, C. Telephone Interview at 12 months' CA – respiratory interval history

Telephone interviews will be undertaken at 6 and 12 months' to obtain limited interval history of respiratory problems including wheezing, medications used, and health services sought for respiratory related problems (Questionnaire in Appendix H).

Fig 1, D. Parental Interview to Ascertain Prevalence of Wheezing and Confirm Risk Factors This parent interview will also be administered by telephone, prior to the regularly scheduled 18-22 month NICHD developmental follow up clinic visit (an NICHD funded, ongoing program). Contacting parents prior to the office visit will help improve the Developmental Follow Up Clinic attendance rate and will allow the clinic visit to provide a back up means to contact the family. All telephone interviews, the 2 limited telephone interviews and the second family history interview at 18-22 months', will be conducted long distance from Rochester (see below). The interview questionnaires are based on questionnaires administered by the Tucson Respiratory Study at approximately one year of age (Questionnaire in Appendix I). Questions are designed to ascertain the frequency and severity of wheezing episodes. In addition, risk factors obtained at the 1st interview will be confirmed or updated.

Fig 1, E. Outpatient Chart Review - Confirm Identity of Primary Care Physician

To confirm results of physician report of wheezing obtained by telephone interview, patients undergoing telephone interview will have their primary care physician's medical record reviewed.

E.1 – Physician report of wheezing

E.2 – Frequency of outpatient pulmonary care. The volume of outpatient pulmonary care including outpatient primary care physician office visits, pulmonary specialty care, emergency room visits, hospitalizations and the number and duration of pulmonary medications will be obtained from primary care physician chart review. To help assure compliance by primary care office staff, a $25 honorarium will be offered for successful completion of the chart review form (45-47).

G.4 Precise definition of primary/secondary outcomes

1) Definition Of Parental Report Of Wheezing. The primary outcome will be parental report of recurrent wheezing, defined as more than 1 episode of wheezing, using questions adapted from the Tucson Children's Respiratory Study, questions validated in a large prospective birth cohort study of term infants (48-54) (Appendices G-I). The primary question used in the telephone interview for this project will be the same as the one used in the Tucson Children's Respiratory Study "Did your child have wheezing?" (48) Additional questions will be used to further characterize the wheezing episodes, identify wheezing associated with a viral illness (parental report of a "cold") and wheezing associated with environmental exposures. The prevalence of health services utilization (outpatient office visits for pulmonary care, ER visits, re-hospitalizations, bronchodilator therapy) for pulmonary reasons will also be collected during interviews. The Tucson study also ascertained frequency of office visits and use of respiratory medications. Of full term infants whose parents reported that their infant had an episode of wheezing, 40% had recurrent wheezing in the first 6 years compared with 22% of infants whose parents reported no episodes of wheezing in the first 3 years.

Parental Report of Wheezing Is A Reliable Outcome Measure of Airway Dysfunction

Evaluation of frequency and severity of respiratory symptoms and volume of pulmonary care has been used as the primary outcome in multiple follow up studies of term and premature infants (10;12;14;43). A recent review evaluated the value of respiratory symptom history ascertained by parental questionnaire in determining the risk for developing asthma in early childhood. By evaluating 9 large, longitudinal, full term birth cohort studies and reviewing the original questionnaire from 7 of these studies, Koopman found that the questions posed to parents

eliciting a history of wheezing in their infants were similar. Parental report of wheezing predicted an increased risk for later respiratory symptoms including asthma. In the studies proposed here, recurrent wheezing ascertained by parental report will be used as the primary outcome, rather than physiologic measurements of airway dysfunction, for several reasons (Table 3). Although the goal of using respiratory questionnaires in the studies proposed here is to measure pulmonary outcome, not to predict asthma, studies of asthma questionnaires and their ability to predict asthma demonstrates the validity of parental report of wheezing as an accurate measure of airway dysfunction.

Reasons to Use Parental Report of Wheezing as Primary Outcome Measure

- Parental interview can be performed more readily on large numbers of patients. The validity of this approach has been shown in several longitudinal studies including The Tucson Respiratory Study, upon which the interview questions are based.
- Recurrent wheezing is highly correlated with changes on pulmonary function testing. In a study of infants with CLD, a history of recurrent wheezing was associated with greater expiratory flow limitation, hyperinflation and airway responsiveness to albuterol on pulmonary function testing compared to those without a history of recurrent wheezing (24).
- Parental recall of respiratory illnesses has been shown to correlate strongly with review of medical office records. For asthma and bronchitis in the past year, Pless et al. found good agreement between recall of 288 parents and physician office chart review. Parental education and occupation were not predictive of a parent's ability to recall the illness (55). In an assessment of parental recall done to evaluate minor injury in children, Harel found recall declined with time, with the best recall occurring in the first 3 months' after injury with further decline after 6 months' from the time of the injury (47;56;57).

Advantages of Conducting Telephone Interviews From a Single Center

Conducting the telephone interviews from Rochester will:

1) require less effort from the individual Network Centers (Network Centers may assist in tracking families)
2) allow standardization of the telephone interview by a core group of trained interviewers
3) blind the telephone interviewer to the SUPPORT Trial study group designation
4) reduce the cost of the study by consolidating the telephone training and follow up at one site.

2) Definition Of Physician Diagnosed Wheezing. A secondary outcome will be physician report of recurrent wheezing, defined as more than 1 episode of wheezing. Physician diagnosed wheezing will be collected by parental report during telephone interviews using the question "Did a doctor tell you your child had wheezing?" and "Where did you see that Doctor, primary care, emergency room, hospital or other?" In addition, review of the primary care physician medical chart will be undertaken to identify episodes of physician documented wheezing.

3) Definitions of Secondary Outcomes - Measures of Volume of Outpatient Pulmonary Care

Important secondary outcomes of outpatient pulmonary morbidity will be collected (Table 1).

Table 1. ***Secondary Outcomes, Covariates and Sources***	
Outcomes	**Source**
Secondary Outcomes	
Number and duration of outpatient pulmonary medications including bronchodilator, diuretic, methylxanthine, and inhaled and systemic steroid therapy.	Family interview, primary care chart review
Number of office visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of emergency room visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of re-hospitalizations for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Growth at 18 months' CA (height, weight and head circumference)	NICHD follow up clinic data

Data Collection: Ascertainment of Outcomes - Field Work

Ascertainment of Wheezing and Outpatient Pulmonary Morbidity By Telephone Interview.
There will be 4 parental interviews over 18-22 months', one prior to NICU discharge and 3 subsequent telephone interviews at 6 month intervals to collect data on the prevalence of recurrent wheezing, need for outpatient pulmonary care, and relevant environmental and family history covariates (Figure 1, A-D above). Based on review of longitudinal studies of full term infants in which follow up patient contacts occurred quarterly to once every 18 months', a 6 month interval for follow up patient contacts is planned in an effort to reduce parental recall omissions which are more likely to occur with less frequent follow up (43;56). The 4 interviews are designed to collect the primary and secondary outcomes of the follow-on study. Other inpatient and outpatient data will be collected as part of the NICHD Neonatal Research Network Generic Database (GDB) and Follow-up Program.

The University of Rochester Neonatology Research Group has conducted similar telephone interview designs as part of an ophthalmologic outcome study of patients enrolled in a randomized trial of cryotherapy to treat ROP and a 15-year, longitudinal neurological assessment conducted by telephone survey among 132 infants treated with surfactant. Telephone follow up rates were 96% follow up at 7 years and 95% follow up at 15 years (58). In the study proposed here, the University of Rochester Health Services Research Group (HSR Group), will conduct the telephone interviews.

In telephone follow up surveys conducted by the HSR Group, follow up rates at 12 months' have exceed 75% in populations at high risk for being lost to follow up (59-65). The Rochester HSR Group has over 2,500 square feet of newly renovated space. Under the direction of Drs. Jonathan Klein and Peter Szilagyi, the HSR group includes sufficient space and all appropriate equipment and personnel to perform telephone interviews and database management for the project presented here. The HSR Group will conduct 3 telephone interviews from Rochester. Drs. Peter Szilagyi and Jonathan Klein, co-directors of the HSR Group, are mentors for Dr. Stevens' K23 Patient Oriented Research Award application. Drs. Klein and Szilagyi will work with Dr. Stevens and Dr. Phelps in the implementation and management of the tracking and respiratory questionnaire program. To facilitate tracking and record keeping, Dr. Stevens will design and write a database to track enrolled patients and their contact information, next scheduled interview, and record answers to phone interview questions. Each interview will close with a question as to whether the family plans a new address or phone number prior to the next interview. The names and phone number of a friend or relative and their primary care physician will be sought so that they may be contacted in the event that contact with the patient is lost. By interviewing families every 6 months', a higher follow up rate will be achieved because family contact information will not become so out of date that the family is lost or that re-contacting them is inefficient. We anticipate that each interview will require 2 hours of staff time, with 20-30 minutes to conduct the interview and 90 minutes to contact family and enter data.

Interview Instruments – (Appendices A-C) Questionnaires based on the Tucson Children's Respiratory Study, a well validated questionnaire used in a large longitudinal cohort study that followed healthy full term infants from birth to over 20 years of age. The questionnaires have been updated to reflect currently available respiratory medications and modified to address the health issues that are faced by formerly premature infants such as use of palivizumab for RSV prophylaxis. In addition, the questionnaires are designed to elicit a thorough history of possible covariates, such as environmental and infectious exposures and family histories of atopy, asthma or respiratory disease.

Physician Office Records Assessment of Wheezing and Outpatient Pulmonary Morbidity Physician office charts will be reviewed to determine physical findings of wheezing, medication use and respiratory related hospitalization history. For primary care pediatricians, the family's consent authorizing release of medical information and an office contact questionnaire will be mailed or faxed to the provider. The questionnaire will be based on a similar document used by the Rochester Research Group to obtain medical information on respiratory issues. To help assure compliance with completing the questionnaire, a $25 honorarium will be offered to the office staff.

Data Collection: Ascertainment of Environmental and Genetic Covariates

Ascertainment of important environmental exposures and genetic risk factors that might confound the relationship between supplemental oxygen exposure and recurrent wheezing will be obtained along with the primary outcome during the same telephone and family interviews (Table 2). A second follow-on study to the SUPPORT Trial, not affiliated with the studies proposed here, is being independently proposed by other investigators to study specific genetic markers that predict greater risk of CLD. Although synergy between our study and the genetic study potentially exists, the genetic study is not yet funded and may not go forward.

Table 2. Postnatal and Genetic Covariates Evaluated as Potential Confounders of Oxygen and Wheezing

Covariates in Home Environment and Exposures The initial questionnaire and 6 month interviews will gather information on other *inhaled exposures* (tobacco, wood stoves, cold air), *residence* (urban vs. rural residence), *infectious exposures* (RSV, palivizumab) and medical risk factors (gastroesophageal reflux, congenital anatomic airway abnormalities)

Covariates in Family History Questionnaires will elicit *family history* of atopy (family history of asthma, eczema or allergy to foods, pets, molds, pollen or dust).

Data Collection: Ascertainment of Primary Exposure

Oxygen Exposure. In the SUPPORT Trial, it is assumed that managing infants with higher vs. lower targeted oxygen saturation range will result in different levels of supplemental oxygen exposure. Because oxygen is the primary exposure in the SUPPORT Follow-on Study and plays a central role in the disease model proposed, oxygen exposure will be quantified carefully. To document the difference in oxygen exposure between groups, FIO2 values will be recorded and analyzed as described in the SUPPORT Trial.

G.5 Sample size estimate with some statistical support based upon primary outcome

The SUPPORT Trial anticipates enrollment of 1506 patients < 28 weeks' gestation, providing 80% power to detect a 10% difference between treatment groups in the incidence of death/CLD and death/stage III Retinopathy of Prematurity (ROP). Assuming mortality of 35% for infants < 1000 grams (NICHD 2002 data), 978 infants would be expected to survive and be eligible for the SUPPORT follow-on study.

Power for detecting a difference between the high vs. low saturation groups for the primary outcome, recurrent wheezing We expect the prevalence of wheezing to be about 0.17 in the low saturation group, and about 0.31 in the high saturation group(12). For the power calculations, we also consider a scenario with a smaller difference between groups: 0.19 for the low saturation group and 0.29 for the high saturation group. We expect the follow up rate to be about 75%, which would result in data on about 733 patients. We also consider a lower follow up rate of 65%, which would result in about 635 patients. Power to detect a difference between groups based on a chi-square test with type I error alpha set at 0.05 is given in Table 7 for each scenario. From those results, we expect to have more than 80% power for the primary outcome. Also of interest are subgroup analyses, where we look separately at the CLD and non-CLD subjects. Of survivors, we expect 37% or 362 infants to have CLD. For the CLD group, we expect the prevalence of wheezing to be about 0.5 in the high saturation group and 0.3 in the low saturation group. If there is a 75% follow up rate, we will have 92% power to detect a difference between the two groups. For the non-CLD subgroup, we expect the prevalence to be 0.2 and 0.1 in the high and low groups, respectively. With 75% follow up, we will have 85% power. Thus, we expect to have adequate power for the primary outcome even in the analyses stratified by CLD.

Table 3. Power for primary outcome, recurrent wheezing.

Follow up rate	Low Saturation	High Saturation	power
75%	0.17	0.31	0.99
75%	0.19	0.29	0.88
65%	0.17	0.31	0.98
65%	0.19	0.29	0.84

We expect the study to be adequately powered for analysis of important secondary outcomes such as use of pulmonary medications. Based on results reported in Davis et al. for infants less than 27 weeks' gestational age [22], we expect the prevalence rate of pulmonary medications to be 0.42 in the high saturation group, and 0.19 in the lower saturation group. In that case, even with a 65% follow up rate, we would have more than 99% power to detect a difference between the groups with a chi-square test. Similarly, the CLD subgroup analyses would have more than 80% power under those assumptions. Based on the power numbers above, we could potentially enroll fewer subjects in the trial and still have adequate power. However, we choose to over enroll slightly to make up for the fact that some patients will likely be lost to follow up.

Data Analysis.
Analysis of primary dichotomous outcomes will be performed by chi square test and presented as a relative risk for development of that outcome. Number of outpatient pulmonary visits for respiratory illnesses will be presented as median values. The Wilcoxon Rank Sum test, a non-parametric alternative to the two-sample t-test, will be used to test for differences between the two groups. Statistical analyses will need to consider the effect of multiple comparison groups on the level of statistical significance. All analyses will be performed in conjunction with the Research Triangle Institute (RTI, North Carolina), the biostatistical support group for the NICHD Neonatal Network. Data will be presented as shown in tables 4-5. Mean FIO2 values in the high and low SpO2 groups will be compared by two sample t-test. Secondary analyses will be done to evaluate the effect of ventilator strategy on pulmonary outcome and presented similarly to table 4 and 5.

Table 4. ***Primary Dichotomous Outcomes***	**Low Saturation**	**High Saturation**	**RR**	**CI**	**p-value**
Parental Report of Recurrent Wheezing (%)					
Physician Diagnosed Recurrent Wheezing (%)					
Need for Outpatient Pulmonary Medications (%)					
Need for Physician Visit for Respiratory Illness (%)					
Need for Re-hospitalization for Respiratory Illness (%)					

Table 5. ***Primary Outcomes – Continuous Outcomes***	**Low Saturation**	**High Saturation**	**p-value**
Number of Physician Visit for Respiratory Illness (Median)			
Number of Emergency Visits for Respiratory Illness (Median)			
Number of Re-hospitalization for Respiratory Illness (Median)			

Expected Results We predict that premature infants managed with a lower targeted oxygen saturation range compared to those managed with a higher targeted oxygen saturation are exposed to lower levels of supplemental oxygen and have reduced risk of recurrent wheezing in the first 18-22 months' CA.

Anticipated Problems and Solutions

1) Participant attrition. As seen in the sample size calculation, the potential for patients to be lost to follow up over time will be offset by over enrolling patients to participate in the follow up. Because patients who enroll in the SUPPORT Trial are randomized, there should be no systematic bias favoring one group over another among patients who are lost to follow up. However, if loss to follow up is in part caused by the treatment or outcomes, this could bias the results. We will therefore investigate whether there are differences in key variables for subjects who are lost to follow up compared to those who remain in the study. For example, we will test whether subjects in one treatment arm were more likely to be lost to follow up than in the other arm. Similarly, we will compare wheezing rates at 6 months' for those who are later lost to follow up compared to those who remain in the study. We do not expect to see any major differences.
2) Low office respiratory health questionnaire response rate. For primary care offices that do not respond to the first mailing, a repeat questionnaire will be mailed. A phone call to the office will be made if there is no response to the second mailing. A $25 honorarium will also be offered to encourage replies.

3) The SUPPORT Follow-on Study of Pulmonary Outcomes has been prepared as the central project for Dr. Stevens' Patient Oriented Clinical Research Grant (K23 Award), submitted 10/1/04. If approved, funds from the K23 will be available to offset a portion of the cost of conducting this SUPPORT Trial Follow-on study. In the event that the K23 is not funded, I will seek additional funding from alternative sources including The American Lung Association and The March of Dimes Foundation.

G.6 Available population/compatibility with other ongoing protocols

Another secondary study proposed by a group independent from ours is looking at the genetics of reactive airways disease in patients enrolled in the SUPPORT Trial. The follow on study proposed here should be complementary to the genetics study, enhancing the both the quality and quantity of data on the prevalence of wheezing and need for outpatient pulmonary care in patients enrolled in the SUPPORT Trial.

G.7 Estimate of projected recruitment time

The recruitment time will be that of the SUPPORT Trial with a 18-22 month period of follow up to ascertain primary and secondary outcomes.

H. RISKS/BENEFITS, WITH ESTIMATE OF FREQUENCY/SEVERITY OF RISKS.

By using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care may be quantified, allowing assessment of whether infants who develop CLD and those who do not have improved pulmonary health as a result of the study intervention. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the follow up visit. We anticipate no risk to the patient of this observational follow on study.

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SUPPORT FOLLOW-ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED AT TIME OF ENROLLMENT
PRIOR TO NICU DISCHARGE

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

QUESTIONNAIRE: ENROLLED CHILD
(Nurse Administered)

Child's Name: _____ Date: ____/____/____
Mo. Day Yr.

Child's Sex 1. Male 2. Female

Child's Birthdate ____/____/____ Apgar ____/____
Mo. Day Yr.

Person being interviewed:

1. Child's Mother
2. Child's Father
3. Both Parents
4. Child's female guardian
5. Child's male guardian
6. Other woman (SPECIFY RELATIONSHIP) _____
7. Other man (SPECIFY RELATIONSHIP) _____

1. At this time, we would like a little information about the environment in which your new child will grow up. First, how many people live with you in your home?

Total household members: _____

2a. After the first few months, will your child be sharing a room with other family members on a regular basis?

1. Yes
2. No

2b. IF YES: How many people will sleep in the same room with him/her? _____

2c. How many living areas are there in your house, excluding closets and bathrooms?_____

3. How many pets are there in the household, either kept inside or out? (RECORD THE NUMBER OF EACH LIVING IN AND OUT OF THE HOUSE).

	Number Kept Inside	Number Kept Outside
Dogs	_____	_____

Cats	_____	_____
Gerbils, Hamsters and Guinea Pigs	_____	_____
Other (Please specify type)		
_____	_____	_____
_____	_____	_____

4. On a scale of 1 to 5, where 1 is not dusty and 5 is very dusty, how dusty would you say your home is compared to other homes in your neighborhood? (CIRCLE APPROPRIATE NUMBER).

Not at all Dusty — Very Dusty

5. Does your home or apartment have air conditioning or some kind of cooling?
   1. Air Conditioning
   2. Evaporative Cooling
   3. Both
   4. None
   5. Other _____
   6. Don't Know

6. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).
   1. Steam or hot water (radiator)
   2. Central gas furnace (furnace)
   3. Electric
   4. Wood Stove
   5. Other
   6. Don't know

7. What fuel is used most for cooking in your home?
   1. Electricity
   2. Gas
   3. Fuel Oil
   4. Wood Stove
   5. Other
   6. Don't Know

8a. Is your child being breast fed? 1. Yes 2. No...SKIP TO QUESTION 9

IF YES,

b. Will this be supplemented with formula? 1. Yes 2. No

c. When do you think the supplement will begin? _____months

d. Do not know when supplements will begin. 1. Yes 2. No

9. Does the mother plan to work outside the home within the next year?
   1. Yes
   2. No
   3. Don't Know

10a. Will your child be cared for by anyone who is not an immediate family member for a major part of the next year?
   1. Yes
   2. No
   3. Maybe

IF YES or MAYBE to 10a:

b. Where will this care be provided?
   1. The parent or guardian's home?
   2. Home of a relative or private sitter?
   3. Day care setting (non-private) ?
   4. Don't Know

c. Will this involve other children, not counting the child's brothers and sisters?
   1. Yes
   2. No

12. Finally, which relative is most likely to have your address in case we lose contact with you?

_____ _____
Name Relationship

_____
Address

_____

SUPPORT FOLLOW ON STUDY
FAMILY HISTORY / FAMILY CONTACT QUESTIONNAIRE - ADMINISTERED PRIOR TO NICU DISCHARGE

1. Name:				
2. Relationship to enrolled child:	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact
3. Age (in years):	________	________	________	________
4. Sex:	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female
5. Does this person currently have:	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
a. Bronchitis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
b. Emphysema?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
c. Bronchiectasis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
d. Asthma?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
e. Inhaled Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
f. Food Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
g. Any other chronic respiratory disease? (SPECIFY)	________ ________	________ ________	________ ________	________ ________
6. How often does this person smoke in the house?	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently

From:	Neil Finer
To:	"Hastings, Betty J."; Higgins, Rosemary (NIH/NICHD) [E]; gaynelle.hensley@utsouthwestern.edu; Wade Rich
Cc:	"Charles Rosenfeld"; "Walid Salhab (Walid Salhab)"; "Zaterka-Baxter, Kristin"
Subject:	RE: SUPPORT OXimeters
Date:	Tuesday, June 14, 2005 10:17:47 PM

Many thanks
Neil

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Tuesday, June 14, 2005 7:29 AM
To: Higgins, Rosemary (NIH/NICHD); gaynelle.hensley@utsouthwestern.edu; wrich@ucsd.edu
Cc: Charles Rosenfeld; Walid Salhab (Walid Salhab); Neil Finer; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT OXimeters

Just a reminder that you will need to send me the Serial Numbers of the oximeters being shipped to UCSD.
Thanks.
Betty

> -----Original Message-----
> **From:** Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> **Sent:** Tuesday, June 14, 2005 10:18 AM
> **To:** gaynelle.hensley@utsouthwestern.edu; wrich@ucsd.edu
> **Cc:** Charles Rosenfeld; Walid Salhab (Walid Salhab); Neil Finer; Hastings, Betty J.; Zaterka-Baxter, Kristin
> **Subject:** SUPPORT OXimeters
>
> Hi Gay
> I spoke with Charles this am and he thought that your site could spare a few oximeters for the UCSD site (they have consents from twins and triplets and not enough oximeters if the moms deliver).
> Wade will send you a FED EX delivery address and let you know how many to send.
>
> Thanks much!!
> Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD)
To: Gaynelle Hensley
Cc: Charles Rosenfeld; Walid Salhab (Walid Salhab)
Subject: RE: SUPPORT OXimeters
Date: Tuesday, June 14, 2005 2:02:00 PM

Gay,
Thanks very much for your help!!
Rose

-----Original Message-----
From: Gaynelle Hensley [mailto:Gaynelle.Hensley@UTSouthwestern.edu]
Sent: Tuesday, June 14, 2005 1:57 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: SUPPORT OXimeters

Rosemary, I am shipping two monitors to Wade. Should arrive tomorrow.
Gay

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 06/14/05 9:18 AM >>>
Hi Gay

I spoke with Charles this am and he thought that your site could spare a few oximeters for the UCSD site (they have consents from twins and triplets and not enough oximeters if the moms deliver).

Wade will send you a FED EX delivery address and let you know how many to send.

Thanks much!!
Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

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6100 Executive Blvd., Room 4B03B

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Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Petrie, Carolyn
Subject: SUPPORT Enrollment.doc
Date: Tuesday, June 14, 2005 8:31:03 AM
Attachments: SUPPORT Enrollment.doc

Rose,
I think Neil wanted to have copies of this to distribute. I can make them and bring them if you want me to. I just enlarged the latest table from the monthly report.

Thanks.
Betty

<<SUPPORT Enrollment.doc>>

NICHD Neonatal Research Network

Monthly Report for the Period Ending 05/31/05

Table 2.17A

Number of Infants Randomized in the SUPPORT Trial
Status of Enrollment by Center

							_Not-Randomized			
Clinical Center	Number Screened	Number Ineligible	Number Eligible	Number Randomized	Percent Random (Random/ Eligible)	Consent Granted (Not Random)	Parent Unavail able	Parent Refused Consent	Consent Not Requested	Physician Refused Consent
3:Case Western Univ.	6	1	5	4	80.00%	1	0	0	0	0
8:Univ. of Miami	2	0	2	2	100.00%	0	0	0	0	0
9:Emory University	1	0	1	1	100.00%	0	0	0	0	0
11:Univ. of Cincinnati	24	0	24	3	12.50%	0	7	9	5	0
12:Indiana Univ.	5	0	5	3	60.00%	0	0	2	0	0
14:Brown University	20	7	13	8	61.54%	0	0	5	0	0
15:Stanford University	2	0	2	2	100.00%	0	0	0	0	0
16:Univ. of Alabama	2	0	2	2	100.00%	0	0	0	0	0
18:Univ. of Texas (H)	20	2	18	9	50.00%	1	0	3	5	0
19:Duke University	2	1	1	1	100.00%	0	0	0	0	0
22:Univ. of Calif. at San Diego	23	5	18	7	38.89%	0	4	2	5	0
	107	**16**	**91**	**42**	**46.15%**	**2**	**11**	**21**	**15**	**0**

From: Higgins, Rosemary (NIH/NICHD)
To: Hastings, Betty J.; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: checks/emails for the SUPPORT secondary
Date: Monday, June 13, 2005 8:33:00 AM

Is this something that is fairly easy to set up? Let me know and we can discuss the possibility.
Thanks
Rose

-----Original Message-----
From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Monday, June 13, 2005 8:29 AM
To: Das, Abhik; Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: FW: checks/emails for the SUPPORT secondary

-----Original Message-----
From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Friday, June 10, 2005 6:05 PM
To: Hastings, Betty J.
Cc: Poole, W. Kenneth
Subject: checks/emails for the SUPPORT secondary

Hi Betty, Ken and Rose,

I may have briefly mentioned this question before, but with the Steering committee meeting coming up, it may be time to think about it more seriously. I am wondering if we could have RTI think about a way to "remind" centers about the important time points for the neuroimaging secondary when it starts up. Specifically, I wonder if we could find a way to generate an email reminder of some kind for centers participating in the secondary that would notify the coordinators and PIs that the 35 week PCA time point is approaching for patients enrolled in SUPPORT. This email could remind the center that, if the patient is enrolled in the secondary, they need to get the near-term cranial US and brain MRI - and also they should arrange to transfer the studies to disk and send to RTI.

Also, Betty thank you again for all the hard work you put in to help me with the forms and manual!

Thanks,

Susan
--
Susan R. Hintz, M.D.
Assistant Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711

fax: 650-725-8351

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; "Rebecca Bara"; bkh@rti.org
Cc: nxs5@cwru.edu; sshankar@med.wayne.edu
Subject: RE: SUPPORT oximeter
Date: Saturday, June 11, 2005 7:04:24 PM

Keep on truckin Betty
Thanks
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, June 10, 2005 12:24 PM
To: Rebecca Bara; bkh@rti.org
Cc: nxs5@cwru.edu; sshankar@med.wayne.edu; Neil Finer
Subject: RE: SUPPORT oximeter

Becky,
Thanks for your help!!!
Rose

-----Original Message-----
From: Rebecca Bara [mailto:ae5357@wayne.edu]
Sent: Friday, June 10, 2005 3:05 PM
To: bkh@rti.org
Cc: nxs5@cwru.edu; sshankar@med.wayne.edu; Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT oximeter

Hi Betty,

A second SUPPORT Study oximeter was sent to Case Western yesterday as an overnight shipment. Oximeter serial # 313415 and docking station serial # 063259.

See you next week,
Becky

From:	Neil Finer
To:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"
Subject:	FW: SUPPORT time in target range
Date:	Friday, June 10, 2005 5:34:38 PM
Attachments:	Time in range for all 6-10-05.rtf Time in range for supp O2 6-10-05.rtf

Please review and we will discuss next week.
Regards
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, June 10, 2005 5:20 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu
Cc: Poole, W. Kenneth; Das, Abhik
Subject: RE: SUPPORT time in target range

Attached is an update on the percent of time babies are kept in the target pulse-ox range, by center. One document is based on all the pulse-ox data we have to date, and the other is based only on days spent on supplemental oxygen (as defined in the e-mail below). Babies in both the high and low treatment groups are included. Please let me know if you have any questions.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone (919) 485-7780
Fax (919) 485-7762
mgantz@rti.org

-----Original Message-----
From: Gantz, Marie
Sent: Thursday, June 02, 2005 4:47 PM
To: 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'
Cc: Poole, W. Kenneth
Subject: RE: SUPPORT time in target range

Hi Neil and Wade,

Attached are two documents showing the proportion of time patients are kept in the target pulse ox ranges at each center. The low and high cases are grouped together. In one document, the numbers are based on all the available pulse ox data. In the other, the numbers are only for days on which we know the babies spent time on supplemental O2. This determination is made using information from form SUPP05. If the baby was intubated/CPAP for >8 hours on a given day and the FiO2 value at 8:00, 16:00 or 23:59 was >.21 or if the baby was on cannula/hood for >8 on that day and FiO2 recorded closest to noon was >.21, then the baby was determined to be on supplemental O2 for that day.

As you will see, we could not identify many records corresponding to days spent on supplemental O2. There are a couple of reasons for this: (1) we have not received forms SUPP05 from some of the centers, (2) we only have information about supplemental O2 for the first 14 days of life, so pulse ox data for days 15 and higher are not included.

Please let me know if you have any questions.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone (919) 485-7780
Fax (919) 485-7762
mgantz@rti.org

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, May 24, 2005 5:38 PM
To: Gantz, Marie
Subject: RE: SUPPORT time in target range

Hello Marie
Many thanks for this data. I will circulate to the Subcommittee first and then decide how to best share with the sites.
Regards
Neil Finer

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, May 24, 2005 2:03 PM
To: wrich@ucsd.edu; nfiner@ucsd.edu
Cc: Poole, W. Kenneth
Subject: SUPPORT time in target range

Neil and Wade,

Attached is a document showing the percent of time babies in the SUPPORT trial have been kept in the target SpO2 ranges. Separate percentages were calculated for the low and high SpO2 arms and for each center. Please note that these are the oximeter display values, not the actual SpO2 values. Also, note that the numbers are based on a very small number of babies. The tables include the number of babies and total number of hours of SpO2 data that went into calculating the percentages. The percent of time in each range is the overall percent of time babies at the center were kept in the range, as opposed to the average percent of time each baby was kept in the range. In other words, babies for whom more data were collected (over a longer period of time) are more heavily weighted in the percent calculations. If you have any questions regarding how these numbers were calculated, please let me know.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone (919) 485-7780
Fax (919) 485-7762
mgantz@rti.org

PERCENT OF TIME SPENT IN EACH RANGE (OXIMETER DISPLAY)
ALL DATA

Center Number	Total number of hours	TARGET <85	>=85 and <88	>=88 and <=92	>92 and <=96	>96
3	1000.5	25.9	7.6	27.7	11.8	27.0
8	171.3	6.2	14.8	54.5	10.1	14.3
11	704.3	9.2	1.9	15.7	20.5	52.7
12	2799.0	16.8	9.1	36.8	16.1	21.2
14	5397.4	11.9	5.6	30.7	12.4	39.4
15	377.5	0.5	0.1	0.8	1.9	96.7
16	1771.8	11.1	4.7	29.1	13.6	41.5
18	526.3	1.0	1.4	23.2	6.3	68.1
22	3371.7	9.9	2.4	17.3	13.7	56.7

PERCENT OF TIME SPENT IN EACH RANGE (OXIMETER DISPLAY)
DAYS ON SUPPLEMENTAL 02 ONLY

Center Number	Total number of hours	TARGET <85	>=85 and <88	>=88 and <=92	>92 and <=95	>95
3	104.1	28.6	10.0	28.9	19.1	13.4
8	171.3	6.2	14.8	54.5	10.1	14.3
14	1139.2	11.1	6.7	43.6	16.5	22.1
15	1.8	11.6	0.9	5.4	13.0	69.1
16	578.8	10.9	6.1	47.3	16.3	19.4
22	913.7	13.9	3.3	25.1	20.4	37.4

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Friday, June 10, 2005 12:26:54 PM
Attachments: SUPPORT_Manual[Updated5-16-05].doc
SUPP11 5-16-05 .doc
SUPP01Screening Log[1-4-05].doc
SUPP02EligibilityForm[1-4-05]Rev.doc
SUPP03DeliveryForm 3-10-05 Rev.doc
SUPP04Admissionto NICU Form[1-4-05]Rev.doc
SUPP05SafetyMonitor[3-10-05]Rev.doc
SUPP06 Prot Dev[1-4-05]Rev.doc
SUPP07Reintubation Form[1-4-05].doc
SUPP08Adverse Event[3-10-05]Rev.doc
SUPP09OutcomeForm[1-4-05]Rev.doc
SUPP10 ROP[3-10-05].doc

Thanks Rose. It's easier for me to send the Word document if that's okay with you.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, June 10, 2005 12:19 PM
To: Hastings, Betty J.
Subject: Re: SUPPORT

Betty
Can you send me the pdf files and we will bring a few copies. Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Hastings, Betty J. <bkh@rti.org>
To: ahensman@wihri.org <ahensman@wihri.org>; mbball@leland.stanford.edu <mbball@leland.stanford.edu>; grisbyca@email.uc.edu <grisbyca@email.uc.edu>; ellen_hale@oz.ped.emory.edu <ellen_hale@oz.ped.emory.edu>; gaynelle.hensley@utsouthwestern.edu <gaynelle.hensley@utsouthwestern.edu>; Georgia E McDavid <Georgia.E.McDavid@uth.tmc.edu>; auten002@mc.duke.edu <auten002@mc.duke.edu>; linda_reubens@urmc.rochester.edu <linda_reubens@urmc.rochester.edu>; lucmille@iupui.edu <lucmille@iupui.edu>; mcollins@peds.uab.edu <mcollins@peds.uab.edu>; Nancy.Miller@UTSouthwestern.edu <Nancy.Miller@UTSouthwestern.edu>; Nancy Newman <nxs5@cwru.edu>; npeters@wfubmc.edu <npeters@wfubmc.edu>; ae5357@wayne.edu <ae5357@wayne.edu>; monica.konstantino@yale.edu <monica.konstantino@yale.edu>; rbridge@ucsd.edu <rbridge@ucsd.edu>; risa.demetrio@sharp.com <risa.demetrio@sharp.com>; kathy.arnell@sharp.com <kathy.arnell@sharp.com>; Reverett@med.miami.edu <Reverett@med.miami.edu>; wrich@ucsd.edu <wrich@ucsd.edu>; (b) (6) >; Lenora Jackson <Lenora.Jackson@uc.edu>; Estelle E. Fischer <estelle.fischer@cchmc.org>; Holly Mincey <minceyhl@email.uc.edu>; Jody Shively <jody.shively@cchmc.org>; Kate Bridges, MD <Kathleen.Bridges@cchmc.org>
CC: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; Petrie,

Carolyn <petrie@rti.org>; Das, Abhik <adas@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>; nfiner@ucsd.edu <nfiner@ucsd.edu>
Sent: Fri Jun 10 12:14:48 2005
Subject: FW: SUPPORT

Dear Coordinators:

Please bring a copy of the latest version of the SUPPORT Manual (updated on May 16, 2005) and copies of the latest versions of the forms. We especially, as all of you are aware, need to discuss the SUP11 form (version 5/16/05). Please bring all your questions for discussion during the time set aside to discuss SUPPORT (from 3-4) on the 15th. If you need a copy of any of this material, please let me know.

Wade and I will bring copies of the questions we have received from some of you.
Thanks.
Betty

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial)

NICHD Neonatal Research Network

Final

Manual of Operations

January 4, 2005
Revised March 10, 2005
Revised May 16, 2005

TABLE OF CONTENTS

Chapter 1

Overview and Trial Design

1.1 Introduction

This manual provides detailed instructions for study procedures related to The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Study): The manual is meant to serve as a reference guide for study staff including investigators, coordinators, technicians, and data managers. The trial objectives and design are summarized briefly below. For further discussion to the study background and design, please refer to the protocol dated August 28, 2004.

1.2 Study Design

This will be a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. The individual factors to be tested will be:

1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early (≤ 1 hour) surfactant and mechanical ventilation.
2) A prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant is no longer requiring ventilatory support or oxygen.

The oxygen saturation monitoring portion of this study will be designed to parallel the planned POST-ROP trial, a multi-center, multinational prospective trial to evaluate different SpO2 levels from birth. The methodology described under oxygen monitoring (**Section 4.1B**) was developed for the current protocol to allow a blinded comparison of 2 different SpO2 levels using specially designed pulse oximeters. These devices will be developed by the Masimo Corporation (Irvine Ca) and tested prior to initiation of this trial, and the POST-ROP study group has agreed to use the ranges described in this protocol, and the methodology that will allow the oximeters to provide actual SpO2 values when the SpO2 is < 85% and > 95% (Personal communication, Cynthia Cole 2004). This methodology will provide the clinicians and caretakers with the infants' actual SpO2 values during hypoxia and hyperoxia, within the current parameters of clinically accepted practice.

Please refer to **Section 8.2** of the Protocol for further Tables describing details regarding the projected outcomes relative to the study interventions

Randomized Intervention	Low SpO2 85% to 89%	High SpO2 91 to 95%
Treatment **Early CPAP**	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control **Prophylactic/Early Surfactant**	Control + Low SpO2	Control + High SpO2

1.4 Primary Hypothesis

1) We hypothesize that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

2) We hypothesize that that relative to infants managed with a higher SpO2 range that the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

1.5 Secondary Hypotheses

We hypothesize that the use of continuous positive airway pressure (CPAP) with a permissive ventilator strategy and/or a lower SpO2 range starting at birth in the delivery room will result in the following:

- A decreased Mortality/NDI at 18-22 months corrected age.
- A decreased frequency of endotracheal intubation before 10 minutes of age
- A decrease of the total duration of mechanical ventilation during the entire NICU stay
- A decreased incidence of surfactant treatment
- A decreased incidence of air leaks on admission and overall
- A decreased duration of intubation
- A decreased duration of mechanical ventilation
- A decreased duration of oxygen supplementation
- A decreased duration of the percentage of pulse oximetry values > 90%
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- A decrease in the percentage of infants who receive postnatal steroids to prevent or treat BPD
- A decreased incidence of BPD at 36 weeks using the physiologic definition of BPD

-
- A decreased incidence of ROP or Stage 3 ROP
- A decreased incidence of necrotizing enterocolitis (NEC)
- A decreased incidence of IVH and severe IVH
- A decreased incidence of periventricular leukomalacia
- A decreased incidence of neurodevelopmental impairment at 18-22 month follow-up
- A decreased incidence of cerebral palsy at 18-22 month follow-up

1.6 Summary of Data Forms

The following is a summary of the data forms used in this study. Further details on each form are provided in subsequent chapters. A complete set of forms can be found in Appendix A.

Screening Log (SUPP01)
A Screening Log (SUPP01) is provided to facilitate the tracking of infants with gestational age 27 6/7 weeks or less for whom a decision has been made to provide full resuscitation as necessary in the Network centers.

Eligibility Form (SUPP02)
This form will be completed for all inborn infants with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimates and who are to receive full resuscitation as necessary.

Delivery Room Form (SUPP03)
Data for this form will be collected in the delivery room and will be completed on all infants.

NICU Admission and Procedures Form (SUPP04)
This form is to be completed on all infants enrolled in the study upon admission to the NICU.

Safety Monitoring Form (SUPP05)
This form is to be completed each day starting with Study day 1 until Study day 14 or outcome status, whichever comes first.

Safety Monitoring Form (SUPP05A)
This form is to be completed if more than one intubation/extubation occurs in the same day.

Protocol Deviation Form (SUPP06)
This form will be completed for all randomized patients whenever a protocol deviation/violation is encountered.

Reintubation Form (SUPP07)
This form will be completed for all intubation/extubations after 14 days.

Adverse Event Form (SUPP08)
This form will be completed for the adverse events, as specified in the protocol, occurring during the initial 14 days of life or study status.

MedWatch Form (SUPP08A)
This form is to be completed in the event of a serious adverse event. It should be faxed to Ken Poole (919) 485-7762 and Rosemary Higgins (301) 496-3790 within 24 hours or the next working day.

Outcome Status Form (SUPP09)
This form will be completed when the infant is discharged home, transferred, if hospitalized at 120 days or death (whichever comes first).

ROP Outcomes and Tracking Summary (SUPP10)
The form will be used to record data for each eye examination (in or outpatient) until both eyes are acute/final.

Physiologic Challenge-Oxygen Reduction Data Form (SUPP11)
This form is to be completed on all infants eligible for oxygen reduction.

Chapter 2

Administration

2.1 Organizational Structure

The NICHD Neonatal Research Network is conducting this study. The Network is funded by the NICHD under cooperative agreements with seventeen institutions comprised of sixteen clinical centers and a data coordinating center. The Steering committee for the Network consists of the Principal Investigator from each clinical center, the data center, and the NICHD project officer. The Steering Committee Chairman is appointed by NICHD and is not a Principal Investigator from any of the Clinical Centers.

2.2 SUPPORT Trial Subcommittee

The SUPPORT Protocol Subcommittee is responsible for the preparation and maintenance of the protocol, data forms, and manual of operations. This subcommittee will monitor the overall study performance (including protocol compliance) and will report the progress of the trial to the Steering Committee. SUPPORT Subcommittee members are:

Neil Finer, MD

Waldemar A. Carlo, MD,

Edward F. Donovan MD

Michele Walsh, MD

Shahnaz Duara, MD

Rosemary D. Higgins, MD

W. Kenneth Poole, PhD

Ruth Everett, RN

Wade Rich, RRT

2.3 Participating NICHD Neonatal Research Network Centers

Centers from the NICHD Neonatal Research Network participating in the trial are listed below. The NICHD center number is indicated in parentheses next to the name of each center and the principal investigator is located in the second column.

PARTICIPATING CENTERS	NRN PI	SUPPORT STUDY PI
Case Western Reserve Univ. (3) Rainbow Babies and Children's Hospital	Michele Walsh, MD	Michele Walsh, MD
University of Texas-Dallas (4)	Charles Rosenfeld, MD	Walid Salhab, MD
Wayne State University (5) Children's Hospital of Michigan	Seetha Shankaran, MD	Seetha Shankaran, MD
University of Miami (8) Jackson Memorial Hospital	Shahnaz Duara, MD	Shahnaz Duara, MD
Emory University (9) Grady Memorial Hospital	Barbara J. Stoll, MD	Susie Buchter, MD
University of Cincinnati (11) University of Cincinnati Hospital	Edward F. Donovan, MD	Vivek Narendran, MD Kurt Schibler, MD
Indiana University (12)	James A. Lemons, MD	Brenda Poindexter, MD
Yale University (13) The Children's Hospital at Yale – New Haven	Richard A. Ehrenkranz, MD	Vineet Bhandari, MD
Brown University (14) Women and Infant's Hospital	William Oh, MD	Abbot Laptook, MD
Stanford University (15) Stanford University Med Center	David K. Stevenson, MD	Krisa Van Meurs, MD
University of Alabama (16) University of Alabama at Birmingham	Waldemar A. Carlo, MD	Waldemar A. Carlo, MD
University of Texas- Houston (18)	Jon E. Tyson, MD	Brenda Morris, MD
Duke University (19)	Ronald Goldberg, MD	C. Michael Cotten, MD
Wake Forest University (20)	Michael O'Shea, MD	Michael O'Shea, MD
Children's Hospital at Strong (21)	Dale L. Phelps, MD	Nirupama Laroia, MD
University of California-San Diego (22)	Neil Finer, MD	Neil Finer, MD

2.3 Responsibilities of the Clinical Centers

The minimum staff required for network participation at each clinical center is the physician Principal Investigator (PI), the Research Coordinator, and a small number of unmasked personnel who will provide 24 hour coverage to monitor study equipment.. The responsibilities of these individuals are described briefly in this chapter and in more detail in subsequent chapters.

The PI or designee is responsible for ensuring the proper conduct of the trial at his or her clinical center (including recruitment and treatment of patients as specified in the protocol),

accurate collection of data and transmission of information to the Data Coordinating Center (DCC). Other specific duties include the following:

- Presenting an in-service to the other physicians
- Applying for IRB approval
- Introducing the study to the parents of prospective patients, and obtaining signed informed consent from the parents of eligible infants (in some centers this responsibility may be delegated)
- Reviewing all infants for whom informed consent has been obtained to confirm their eligibility
- Informing the IRB of the study progress.

The Research Coordinator will be responsible for the day-to-day operations of the study at the clinical center, including data collection and management. This responsibility includes the following:

- Presenting an in-service to the appropriate nursing and ancillary staff detailing the study protocol
- Collecting information necessary to complete the data collection forms, and coordinating data entry
- Training and certifying the staff in the use of the network microcomputer
- Controlling access to the network microcomputer and ensuring that required back-up, security and confidentiality are maintained
- Responding to edit messages and other communications from the data center
- Distributing updates of the protocol and of the manual of operations to clinical center staff
- Achieving and maintaining fluency with the procedures for obtaining the treatment group assignment from the data center
- reporting deviations to the data center within 24 hours of occurrence

2.4 Responsibilities of the Data Coordinating Center

The DCC is responsible for all aspects of statistical design and analysis as well as data management of the study. In particular, this includes:

- Processing, updating and distributing the protocol and manual of operations
- Developing, printing and distributing the data forms, including periodic updates as necessary
- Developing, testing and implementing the database and other software. Ensuring that data are correct and complete by implementing editing and auditing procedures
- Monitoring the progress and quality of the study
- Preparing interim and final analyses and reports
- Participating in the preparation of presentations and publications relating to the study.

2.5 Responsibilities of NICHD

In addition to its role as a funding agency, the NICHD participates in the activities of the cooperative agreement by being represented on the Steering Committee. The Program Official also participates in the development of protocol and in assisting the Steering committee in the coordination of the studies conducted by the Network. The NICHD Program Official, in conjunction with the RTI Principal Investigator is responsible for monitoring site performance of all participating centers. The Program Official has the following responsibilities:

- Assistance in the development of the study protocol.
- Assistance in the development of capitation-based budgets, including the identification of study costs and special institutional needs.
- Allocation of network resources to meet study needs including pharmacies, study drug supply, and other special requirements of the study.
- Facilitation of training meetings, site visits, and subcommittee meetings.
- Participating in preparation of publications.

Chapter 3

Screening, Eligibility, Consent

3.1 Study Population

Study subjects are inborn infants of 24 0/7ths to 27 6/7th weeks at birth for which a decision has been made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) will be enrolled.

3.2 Inclusion Criteria

- Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
- Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Infants without known major congenital malformations

3.3 Exclusion Criteria

- Any infant transported to the center after delivery
- Infants born during a time when the research apparatus/study personnel are not available

3.4 Informed Consent

Infants will be recruited for this study by approaching one or both parents at the time of admission to the hospital at risk for premature delivery at 27 weeks or less. It is anticipated that, whenever possible, the parents will be approached by study personnel to discuss the trial and obtain an informed consent for the participation of the infant at delivery. As discussed in Section 4.1, randomization will be by family, thus all offspring will be randomized to the same trial arms, provided adequate equipment and personnel are available at the time of delivery.

3.5 Screening Procedures

All admissions for threatened premature delivery will be screened on a daily basis to ensure that eligible patients can be enrolled. Obstetrical colleagues at each participating institution will be informed of the nature of this study and encouraged to discuss this study with their patients at risk of premature delivery. The study coordinator at each site will maintain a screening log of potentially eligible patients. In addition the usual practice of neonatal consultation for all such at risk deliveries will provide a second opportunity to approach mothers with fetuses at risk of preterm delivery.

Chapter 4

Randomization

4.1 Randomization Procedures

Randomization will be stratified by gestational age group (24 - 25 6/7 and 26 - 27 6/7) and will occur prior to delivery for consented deliveries. The randomizations will be performed by **utilizing specially prepared envelopes**. The Data Center will prepare brown sealed envelopes which will contain the identity of the treatment combination to be assigned the infants enrolled into the study. **Deliveries will be randomized as a unit, thus multiples, twins, triplets etc will be randomized to the same arm of the trial.** One envelope will correspond to the delivery of a consenting mother regardless of the number of babies delivered so that all babies from a given delivery will receive the same treatment combination.

4.1.1 Randomization and Masking, Storing and Assigning Oximeters

Two sets of envelopes will be used; one for the gestational age group 24 -25 6/7 weeks and one for the 26 - 27 6/7 week gestational age group. These should be kept in separate boxes or drawers with the group clearly indicated **(this will be noted on the label on the front of the envelope).** The envelopes will be sequentially numbered with a randomization number on the outside of the envelope so they can be selected in the order of use to maintain a balancing of the treatment assignments. These envelopes are to be stored in a secure place in or near the delivery for quick accessibility.

The envelope should be selected, from the appropriate group, and opened at the time of delivery by a study staff member only when the delivery is imminent. Inside the sealed envelope will be a white card which will contain the randomization number and treatment assignments. The card will indicate which of the Early CPAP/Early Surfactant treatments is selected and will indicate a color code for the High/Low SpO2 arm of the study. They will be specified as one of the following:

- **Treatment Group** (EARLY CPAP and permissive ventilation management) with an **Oximeter code** of either **Blue or Orange**
  OR
- **Control Group** (Early SURFACTANT and conventional ventilator management) with an **Oximeter code** of either **Blue or Orange.**

The **Blue/Orange codes** will designate an assignment to either the **Low (85% - 89%)** or **High (91% - 95%)** SpO2 group. The oximeters will be shipped directly to the clinical sites from Masimo. The Data Center will supply the sites with the **Blue and Orange** labels and these color coded labels will correspond to the serial numbers on the oximeter(s). The serial number(s) will need to be recorded on the appropriate data form (**SUPP04 Form)**.
Note: The oximeters should be stored in such a manner that the individual who will be obtaining them and returning them to their original location can easily identify which oximeters belong to which color-coded randomization group. It is not recommended that the oximeters be

identified with the blue or orange colored labels. A system whereby the serial numbers for each color group are identified at the storage sight, along with a list of which infants have been placed on which serial numbers, makes it possible to track oximeters without using the color coded labels on the devices themselves.

The person opening the envelope should announce to the team the assignment of the Early CPAP/Early Surfactant arm of the study. Someone should then take the opened envelope to the secure area where the oximeters are stored and select the oximeter (s) whose color code is specified in the randomization envelope. **Once the envelope is opened, it should be stored in a secure location only accessible to staff with "a need to know".** Randomization should be done only if sufficient numbers of oximeters of both types (i.e. high and low SpO2) are available to accommodate the delivery.

Once the use of an oximeter has been completed, it should be returned to the color coded location for storing the inventory of oximeters (e.g., a color coded shelf) checking to be sure that the serial numbers match. A log should be maintained to record the date and time the particular oximeter is returned to this location.

Chapter 5

Study Interventions

5.1 Study Intervention A

5.1.1 Mode of Ventilatory Support

The intervention will begin after birth when the infant is given to the resuscitation team. The conduct of the resuscitation will follow usual guidelines. Once stabilized:

- All **Control infants** in both strata will receive prophylactic/early surfactant (within 1 hour of age).
- All **Treatment infants** will be placed on CPAP/PEEP following stabilization, and will be intubated only for resuscitation indications.

The assignment to either a high or low SpO2 by **Study Oximeter Assignment** will be performed immediately following NICU admission, with a maximum allowable delay of 2 hours following NICU admission.

Treatment Groups

5.1.2 CPAP Group: Early Extubation and CPAP – Both Strata

5.1.3 Delivery Room Management

1) FiO2:
Standard of care

2) CPAP:
CPAP or ventilation with PEEP will be utilized if the infant requires positive pressure during resuscitation. CPAP will be continued until admission to the NICU using the Neopuff or equivalent device and a face mask or nasal prongs. Initial PPV will be at a PIP of 15-25 cm H_2O and a PEEP/CPAP of 5 cm cmH_2O. High flow nasal cannula (e.g. Vapotherm) may not be used as the primary mode of therapy for infants randomized to Early CPAP in the first 14 days.

3) Intubation:
Infants may not be intubated for surfactant only in the DR. Infants who require intubation for resuscitation will receive surfactant within 60 minutes of birth. Intubation will be performed only for the standard NRP indications including failure to respond to PPV with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determines that surfactant is urgently required.

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

5.1.4. NICU Management

These infants will be managed on nasal CPAP and intubation is never required by protocol. They ***MAY*** be intubated if they meet ***ANY*** of the criteria listed below. If intubated within the first 48 hours of life they should receive surfactant.

1. Intubation:

- An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
- A $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) documented on a single blood gas
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation.)

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

These criteria will continue in effect for a minimum of 14 days of life.

Intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.
(e.g. - Upper airway obstruction (choanal atresia, micrognathia/glossoptosis)).

2. Extubation:
An intubated CPAP-Treatment infant ***MUST*** have extubation attempted within 24 hours if ***ALL*** of the following criteria are met and documented on a single blood gas:

- $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples)
- An indicated SpO2 $\geq$ 88% with an FiO2 $\leq$ 50%
- A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving ionotropic/vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA

These criteria will continue in effect for the first 14 days of life.

*Failure to extubate an infant meeting all of the above criteria will be recorded as a study protocol violation (**on the SUPP06 Form**) unless extenuating circumstances are noted (e.g. PIE, airleak).*

3. Reintubation

If a Treatment infant is extubated as per Protocol Criteria, and requires re-intubation for any indication, any further attempt at extubation may be delayed for 24 – 48 hrs based on the clinician's decision.

Re-intubation criteria are the same as those for Intubation for the CPAP infants. Thus, intubation is not required, but these infants ***MAY*** be reintubated if they meet ***ANY*** of the following:

4. Re-Intubation Criteria:

- An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
- A $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) on a single blood gas
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. Note that clinically defined shock is an accepted indication for intubation.

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Re-intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.

5. D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be discontinued earlier and follow unit Standard of Care. May be restarted at any time in such infants.

CPAP infants who require intubation three times, for any criteria, will have all subsequent treatment including subsequent extubations and any further re-intubations performed using unit Standard of Care. This addition is to prevent such infants from being exposed to further protocol driven intubations and extubations.

6. Surfactant

Infants intubated in the first 48 hours for respiratory distress should be given a minimum of one dose of surfactant. Up to 4 surfactant administrations may be given if the FiO2 is greater than 50% following manufacturers' recommendations for dose and dosing interval.

5.1.5 Explanation:

The purpose of the above criteria is to minimize the duration of intubation of Treatment infants. The Criteria for extubation are more severe than those of the Control Group infants, and extubation must be attempted for any infant who fulfills the stated criteria.

The criteria for re-intubation recognize that intubation is traumatic, and is designed to avoid frequent attempts at extubation for infants who fail.

5.1.6 Control Group- Prophylactic/Early Surfactant and Ventilation

5.1.7 Delivery Room Management:

Infants will be intubated in the delivery room and given surfactant or receive surfactant within 60 min minutes of birth. The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

5.1.8 NICU Management:

1. Extubation:

An intubated Surfactant-Control infant will continue to receive mechanical ventilation until extubation criteria are satisfied, but **MUST** have extubation attempted within 24 hours of fulfilling ***ALL*** of the following criteria documented on a single blood gas:

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 ≤.35 with a SpO2 ≥ 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving ionotropic / vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA (Defined as bounding pulses, audible murmur and Echo confirmation of L-R shunting with increased LA/Ao size

These criteria will continue in effect for a minimum of 14 days for all infants.

Failure to attempt to extubate an infant meeting all of the above criteria, or extubation prior to reaching criteria, will be recorded as a study protocol violation ***(on Form SUPP06)*** *unless extenuating circumstances are noted.*

2. Weaning

This protocol will not define strict weaning criteria for the Control infants, but it is to be understood that reasonable attempts should be made to extubate these infants. While it is understood that some centers may be using somewhat more severe FiO2 and PaCO2 criteria than those listed here as current practice, these Criteria are thought to reflect current Network practice and practice at 2 of the 3 Best practice centers.

3. Reintubation:

- Control Infants may be reintubated using Standard of Care.

5.1.9 Explanation:

Control infants are to be treated using an approach considered similar to current standards of care. Apparatus for resuscitation for Control Infants at each center will represent their usual

equipment for the resuscitation of an ELBW infant. The Neopuff may be utilized for such infants as above, but this is not mandatory. It is anticipated that the majority of these infants will be intubated and receive surfactant in the delivery room.

5.2 Study Intervention B

5.2.1 Low versus High SpO2 Range:

There will be 2 ranges of SpO2 utilized during this trial. The Low target range will be 85% to 89% and the High target range will be 91% to 95%. The altered Pulse Oximeters (PO) as described below will display a range of 88% to 92% when the SpO2 ranges are in the Target ranges indicated above. Thus a Low range PO will read 88% when the actual SpO2 is approximately 86%, and 92% when the actual SpO2 is 89%. Similarly the High range PO will display 88% when the actual SpO2 is 91% and indicate 92% when the actual SpO2 is approximately 95%. As an added safety feature, the POs used in this trial will gradually revert to the actual SpO2 values and allow the caretakers to be aware of actual SpO2 values < 85% and > 95%.

5.2.2 Low Range Infants:

These infants will be monitored with a target SpO2 range of 85% -89% with suggested indicated alarm limits of 85% and 95%, representing approximately a 10% span for alarms as long as the infants are receiving any ventilatory support, CPAP, and/or supplemental oxygen.

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

5.2.3 High Range Infants:

These infants will be monitored with a target SpO2 range of 91% -95% with suggested indicated alarm limits of 85% to 95% representing approximately 10% span for alarms as long as they are receiving any ventilatory support, CPAP and/or supplemental oxygen.

The study pulse oximeters will be removed once the infant has been in room air for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until discharge 36 weeks PCA.

These interventions will be delivered using specially developed pulse oximeters whose displays will be adjusted so that the randomized range of SpO2 (either 85%-89%, or 91%-95%) will be indicated by a range of 88%-92%. These POs will be able to display trend plots of the SpO2 display for a preceding interval to allow the caretakers to receive feedback regarding the actual SpO2 ranges of their baby.

The suggested alarms limits will be 84% to 96% for both groups. All values outside of alarm limits will be unaltered values.

The target oxygen saturation (88-92%) of the display will be the same in both groups as indicated in Table 1 below.

Table 1

Output and Actual SpO2 Targets and Alarms

Group	Display Target	Actual Target	Alarm Values
Low SpO2 range	88-92%	85-89%	<85 and >95%
High SpO2 range	88-92%	91-95%	<85 and >95%

Every 30 days until 36 weeks PCA, or until the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per 10 seconds of monitoring) will be downloaded and transmitted to RTI for subsequent analyses to determine that were are within the desired ranges. (This interval of sampling may change to a less frequent interval for the convenience of the study personnel, without loosing significant data). These data points will be used to confirm that the infants were managed at the target ranges and provide objective confirmation of the SpO2 Group assignments. The technology for downloading and interpreting this data was used in the DR CPAP Pilot trial, but recent technology utilizing a software program (Profox, Profox Inc, Escondido, Ca) which has been written to facilitate this process, will dramatically simplify this procedure.

All ventilatory care after 14 days of age will follow the standard of care for each unit. Each unit will provide guidelines for their approach to continuing mechanical ventilation.

See Flow of Study Intervention on page 5.7:

Flow of Study Intervention

	Early Extubation and CPAP	Prophylactic/Early Surfactant and Ventilation
Delivery Room Management:	• Resuscitate using CPAP. If necessary, initial PPV settings PIP 15-25, PEEP 5. • Transport on CPAP **If intubated for resuscitation** • Give surfactant within 1 hour of age. Do not intubate unless indicated by NRP guidelines	• Intubate and give surfactant within 1 hour of age • Transport with PPV according to SOC
Upon NICU Admission:	Randomize within 2 hours to Pulse Oximeter	Randomize within 2 hours to Pulse Oximeter
Intubation Criteria:	**May intubate for ANY of these criteria** • FiO_2 >.50 required to maintain indicated SpO2 ≥ 88% (using the altered Pulse Oximeters) for one hour • $PaCO_2$ > 65 torr (art. or cap. samples, if venous $PaCO_2$ > 70 torr) documented on a single blood gas • Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. **If intubated, give surfactant within the first 48 hrs if in respiratory distress**	**Reintubation Criteria:** **Standard of Care**
Extubation Criteria:	**Attempt extubation within 24 hours of fulfilling all of the following criteria:** • $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples) • An indicated SpO2 ≥ 88% with an FiO2 ≤ 50% • Mean airway pressure (MAP) < 10 cm H_2O, vent rate ≤ 20 bpm, amplitude < 2X MAP if on HFV • Absence of clinically significant PDA • Hemodynamically stable	**Attempt extubation within 24 hours of fulfilling all of the following criteria** • $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples) • FiO2 ≤ 35 with SpO2 > 88% • Mean airway pressure (MAP) < 8 cm H_2O, vent. rate ≤ 20 bpm, amplitude < 2X MAP on HFV • Absence of clinically significant PDA • Hemodynamically stable
Repeated Surfactant Doses:	Subsequent doses may be given at the manufacturer's recommended dose up to a total of 4 doses.	
Intubation:	Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.	
CPAP D/C:	In room air for at least 1 hour	
CPAP Resumption:	At any time	
Duration of Intervention:	14 Days	14 Days

5.3 Delivery of Interventions

5.3.1 CPAP/PEEP in the DR

CPAP and positive pressure ventilation (PPV) in the delivery room for Treatment infants will be administered via a T-piece resuscitator a neonatal ventilator, or an equivalent device that is currently used by the site for the delivery of CPAP.

5.3.2 Use of Nasal SIMV

For uniformity nasal SIMV may be used in place of CPAP ***only following extubation*** for both Treatment and Control infants.

5.3.3 Use of Caffeine

Caffeine may be administered 2 hours prior to planned extubation, and for any clinically significant apnea.

5.3.4 Surfactant Type

All centers are asked to follow current unit practice in determining the type of surfactant utilized and manufacturers' recommendations for re-dosing intervals.

At least one dose of surfactant **must** be administered to any infant intubated within 48 hours of birth, with evidence of respiratory distress, who has not previously received surfactant.

5.3.5 Postnatal Steroids

Postnatal steroids for the purpose of preventing or treating BPD/CLD will be prohibited for any infant in this trial in the first 21 days of life. Hydrocortisone for hypotension may be used as noted below.

If postnatal steroid use is considered after 21 days of life for any infant for the prevention/treatment of established lung disease the following guidelines should be followed:

1. The AAP statement and recommendations regarding Post-natal steroids should be adhered to.
2. The lowest dose of dexamethasone considered effective should be used and if ineffective after 24 – 48 hours they should be stopped.
3. Consider using hydrocortisone as a first therapy at a dose of 1 -2 mg/kg/day before using dexamethasone.
4. For hypotension, hydrocortisone in a dose of 1 mg/kg/dose should be given after fluid administration and standard doses of ionotropes/pressors have failed to correct the low blood pressure.

5.3.6 Head Ultrasound

If a Head ultrasound is done between days 4 and 21 the results will be recorded for this study. If one is not done for standard of care, the study requires that at least one HUS be completed during this window.

5.4 Protocol Violations

The occurrence of any one of the following criteria will determine whether an individual infant will be considered a protocol violation:

1. Intubation of an Early Extubation and CPAP infant in the DR for the exclusive purpose of giving surfactant, in the absence of bradycardia (HR< 100 bpm) and/or poor color or an SpO2< 85-90% in an infant with adequate spontaneous respirations or receiving adequate ventilation
2. Failure to continue CPAP on admission to the NICU for an Early Extubation and CPAP infant requiring `supplemental oxygen
3. Intubation and surfactant administration of an Early Extubation and CPAP infant without meeting stated protocol criteria.
4. Failure to extubate an Early Extubation and CPAP infant who fulfills all the extubation criteria.
5. Extubation of a Prophylactic/Early Surfactant and Ventilation infant who does not meet any of the extubation criteria.

All protocol violations will be reviewed by the center PI who will discuss each protocol violation with the involved clinicians and provide a written summary including steps taken to avoid future violations. The Protocol Violation/Deviation Form (SUPP06) should be completed each time a violation/deviation is encountered.

5.5 Adverse Events

Serious and unanticipated adverse events may be anticipated in this vulnerable population. Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades III-IV, Papile)
4. Pulmonary hemorrhage
5. Nasal breakdown requiring discontinuation of nasal prongs
6. Death

These outcomes will be evaluated on a monthly basis by RTI using sequential analysis boundaries, and if the incidence of any of these outcomes differs among the treatment arms of the study this information will be provided to the DSMC for immediate evaluation and consideration of termination of the study or treatment arm. The SUPPO8 (Medwatch Form) should be completed in the event of a serious adverse event. It should be faxed to RTI (919) 485-7762 and Rosemary Higgins (301) 496-3790 within 24 hours or the next working day.

Chapter 6

Screening Log

6.1 Instructions for completing the Screening Log (SUPP01)

Each center will implement an effective and efficient screening procedure to identify all potential study subjects. A Screening Log (SUPP01) is provided to facilitate the tracking of infants with gestational age 27 weeks or less for whom a decision has been made to provide full resuscitation as necessary. The following information is used to identify each infant and is placed on the screening log.

Center Number
Each study center has been assigned a Network center number.

Site
Centers with more than one participating hospital also have a site code (A, B, C or 1, 2, 3).

THE FOLLOWING INFORMATION WILL BE FILLED OUT WHEN THE MOTHER IS FIRST SCREENED:

Mother's Last Name
The last name of the mother who is being screened should be written on this log. This confidential information is recorded for the convenience of the center and must not be submitted to the DCC.

Mother's Hospital Number
The hospital number of the mother should be recorded. This confidential information is recorded for the convenience of the center and must not be submitted to the DCC.

Gestational Age
Record the actual gestational age in weeks and days when the mother is identified.

Last Date Eligible
Record the date this mother will reach 27 6/7 completed weeks. This will be the date when her infant would no longer be eligible for enrollment in this study. This will be used as a guide to track a mother who may be at risk for premature delivery but who may not deliver within the window of the study.

Consent
Record 'Y' or 'N' if consent has been obtained. If consent is obtained this pregnancy/infant birth will be followed to determine eligibility.

THE FOLLOWING INFORMATION WILL BE FILLED OUT ON THOSE PATIENTS WHO HAVE GIVEN CONSENT WHEN THE INFANT IS BORN WITHIN THE ELIGIBLE WINDOW:

Date of Birth

Enrolled in Study
Record 'Y' or 'N' if infant was enrolled in this study. This will ensure that all potential infant outcomes were identified (including but not limited to: enrolled in the study, gestational age at birth >28 weeks, died in delivery room).

Network Number

Record the Network number of any infant enrolled in the study.

Chapter 7

Eligibility Form

7.1 Instructions for completing the Eligibility Form (SUPP02)

Heading- Infant's Identification
The following information is included in the heading section of all patient specific data forms: Center, Site, Network Number, Birth Number and Mother's Initials **(optional).**

7.1.1 Form Section A: Eligibility Criteria

If any criteria are not met, the infant is ineligible.

1. Inborn infant with a gestational age of 24 weeks 0 days to 27 6/7th completed weeks by best obstetrical estimate?
Code yes if the infant was 27 completed weeks or less by best obstetrical estimate or by appropriate clinical examination.

2. Infants who will receive full resuscitation as necessary?
Code yes if the infant will require full resuscitation as necessary

3. Infant who does not have know major congenital malformations?
Code yes if the infant does not have known major congenital malformations.

If any of the above questions are answered No the infant is NOT eligible.

7.1.2 Form Section B: Exclusion Criteria

1. The infant was born during a time when the research apparatus/study personnel are not available?
Code yes if there was no apparatus/study personnel available.
If Yes, indicate the reason:
1= Equipment not available
2= Personnel not available

7.2 Form Section C: Consent

Sample consent forms for this study are included in Appendices D and E.
Consent status:

Answer this question with one of the following codes, according to the following definitions:

0 = Not Eligible
Code '0' if one or more of the eligibility criteria questions are answered "No". If the infant is ineligible, regardless of whether consent was granted or not, this code should be used.

1 = Consent Granted
Code '1' if parenteral/guardian consent is obtained.

2 = Parent Unavailable
Code '2' if the parent or legal guardian is unavailable throughout the eligibility period

3 = Parent Refused Consent
Code '3' if a parent or legal guardian refuses consent.

4 = Consent Not Requested
Code '4' if consent for this study was not requested. Language or social problems as well as enrollment in conflicting trials should be recorded here.

5 = Physician Refused Consent
Code '5' if the infant was eligible for the study, but the attending physician refused to consider the baby for enrollment.

If the consent status is 3, 4, or 5, indicate the reason why consent was refused or not requested.

If the patient is eligible and consent is granted, but the patient is not randomized, indicate the reason why the eligible infant was not randomized into the study although consent from both parent/guardian and physician was obtained.

7.3 Form Section D: Randomization

An infant is eligible for randomization if all eligibility criteria are answered Yes in Section A. The infant is considered randomized at the time the randomization number is given.

1. **Was infant randomized into the study?** Record "Yes" if the infant was randomized into the study.
   If No, indicate the reason the infant was not randomized.
   If Yes,
   a. Date of Randomization- Enter the date on which the randomization envelope was opened to enroll the infant into the study. All dates for this study are recorded using the MM/DD/YYYY format.
   b. Time of Randomization- Enter the local time at which the envelope was opened to randomize the infant.
   c. Randomization Number-Enter the randomization Number. This number is recorded on the SUPP02 during the randomization. The randomization numbers are four digit numbers with a different set of numbers, stratified by gestational age, for each group. There will be a group with gestational age from 24 - 25 6/7 weeks and a group with gestational age 26 to 27 6/7 weeks. The groups for each Center will be as follows:

   24 - 25 6/7 weeks = 3001 - 3160
   26 - 27 6/7 weeks = 4001 – 4160

   d. Treatment Assignment:
   Enter 1= Early Extubation and CPAP or 2= Early Surfactant and Ventilation

   e. Oximeter Color Code
   Enter 1= Blue or 2=Orange

   All times for this study are recorded using the 24-hour clock format (00:00 to 23:59).

Chapter 8

Delivery Form

8.1 Instructions for completing the Delivery Form (SUPP03)

8.2 Form Section A: Delivery Room Information

1. Date and time of Delivery

a. Date:

Record the date on which child was born (day begins at 00:00, ends at 23:59).

b. Time:

Use a 24-hour clock with midnight coded as 00:00.

2. Was CPAP initiated in the DR? An application of CPAP will be considered the fitting of a mask over the infant's airway without intermittent positive pressure breaths or the placement of nasal prongs.

Record 'Y' if CPAP was initiated in the DR

a. If Yes, time of CPAP initiation

Use the 24-hour clock with midnight coded as 00:00

b. Device: Record Device.

1= Neopuff
2= Ventilator
3=Anesthesia Bag
4= Bubble
9 =Other

If Device is 5, specify the type.

3. Was positive pressure ventilation (PPV) initiated in the DR? PPV is defined as the administration of intermittent positive pressure breaths using either a mask or endotracheal tube.

4. Was positive end-expiratory pressure (PEEP) used in the DR?

Record 'Y' if PEEP was used in the DR

a. Maximum PEEP:

Record the maximum PEEP level as cm/H_20

5. Was intubation attempted in the DR?

a. **If Yes, was the intubation successful?**

Code Yes if the intubation was successful.

6. Indication for intubation

Record the indication for intubation;

1= Surfactant administration

2= Resuscitation
3 = Other (specify)
4 = As required by randomization assignment
Code 4 will be used to indicate that the infant was intubated because of the protocol assignment of Early Surfactant.

If for (2) Resuscitation
a. Low HR? Record Yes if the infant was resuscitated because of low HR.
b. Poor color? Record Yes if the infant was resuscitated because of poor color.
c. Apnea? Record Yes if the infant was resuscitated because of apnea.
d. Other? Record Yes if the infant was resuscitated for any other reason and specify the reason.
If for (3) Other, specify the indication for intubation.

7. Did the infant receive surfactant in the delivery room?
Record 'Y' if the infant received surfactant in the DR.
If Yes, Date and time of surfactant administration
a. Date: Record the date of surfactant administration using the mm/dd/yyyy format.
b. Time: Record the time of surfactant administration using the 24-hour clock with midnight coded as 00:00.

c. Type: Record the type of surfactant given
1= Infasurf
2= Curosurf
3= Survanta
4= Exosurf
5= Other, specify the type.

8. Was active resuscitation required? Record 'Y' if active resuscitation was required which would include bag and mask ventilation and/or intubation in the delivery room.
If Yes,
a. Chest compressions?
Record 'Y' for external pressure over central chest to contract heart.
If Yes,
1. Duration: Record the duration of chest compressions in minutes.
b. Epinephrine?
Record 'Y' if Epinephrine was provided to the infant at the time of birth irrespective of route (intratracheal or intravenous)
1. Number of doses: Record the number of doses the infant received.

9. Status following resuscitation:
Record 'the status of the infant at delivery.
1= Admitted to the NICU for further care
2= Infant died

Chapter 9

Admission to NICU Form

9.1 Instructions for completing the Admission to NICU Form (SUPP04)

The purpose of this form is to determine if the study interventions are applied as per the protocol

9.2 Section A. NICU Admission

1. Date and time of admission to the NICU:

a. Date: Record the date the infant was admitted to the NICU. Day begins at 00:00, ends at 23.59

b. Time: Record the time the infant was admitted to the NICU using the 24-hour clock with midnight coded as 00:00.

2. Respiratory support on admission to the NICU:

Record the respiratory support as:
1= HVF
2= CV
3= Nasal SIMV
4= CPAP
5= NC
6= Hood
7= No Support

3. SaO_2

Record the infant's SaO_2 on admission to the NICU.

4. FIO_2

Record the infant's FiO_2 on admission to the NICU.

5. Was a blood gas done after admission to the NICU?

If Yes, Record the first blood gas obtained following the NICU admission:

a. Date: Record the date the infant was admitted to the NICU. Day begins at 00:00, ends at 23.59

b. Time: Record the time the infant was admitted to the NICU using the 24-hour clock with midnight coded as 00:00

c. Source: Record the source of the first blood gas
1= Arterial
2=Venous
3= Capillary

Record the results of the first blood gas.

d. pH:

e. pCO_2:

f. pO_2:

g. FiO_2:

6. Date and time the study oximeter was placed on this infant.
Record the date and time:

a. Date: Record the date the infant was admitted to the NICU. Day begins at 00:00, ends at 23.59
b. Time: Record the time the infant was admitted to the NICU using the 24-hour clock with midnight coded as 00:00
c. Serial Number: Record the serial number that is pre-labeled on the oximeter.

9.3 Section B. NICU Procedures

1. Was the infant intubated for the first time after admission to the NICU within the first 14 days?

If Yes, Record the date and time:

a. Date: Record the date the infant was admitted to the NICU. Day begins at 00:00, ends at 23.59
b. Time: Record the time the infant was admitted to the NICU using the 24-hour clock with midnight coded as 00:00

c. Indication for intubation:

1. Surfactant?
2. $FIO_2 > .50$ to maintain $Sa0_2 \geq 88\%$?
3. $PaC0_2 > 65$ on single blood gas?
4. Apnea requiring bag and mask ventilation?
5. If No to all above, state reason:

Record reason:
1= Hemodynamic instability
2= Clinical shock/sepsis
3= Other reason, If other, specify other reason.

2. Was a blood gas done within 30 minutes prior to intubation?

If Yes, Record the date and time:

a. Date: Record the date the infant was admitted to the NICU. Day begins at 00:00, ends at 23.59
b. Time: Record the time the infant was admitted to the NICU using the 24-hour clock with midnight coded as 00:00
c. Source: Record the source of the first blood gas
1= Arterial
2=Venous
3= Capillary

Record the results of the first blood gas.
d. pH:
e. $pC0_2$:
f. pO_2:
g. FiO_2:

3. Was Surfactant given in the NICU?

If Yes, Record the following for each dose:

a. Date: Record the date the infant received the first dose of surfactant in the NICU and for the first 14 days. Day begins at 00:00, ends at 23:59

b. Time: Record the time the infant received the first dose of surfactant in the NICU using using the 24-hour clock with midnight coded as 00:00

c. Type: Record the type:

1= Infasurf
2= Curosurf
3= Survanta
4= Exosurf
5 = Other, If other, specify type.

Chapter 10

Safety Monitoring Form

10.1 Introduction

Daily outcome data will be collected for Study Days 1-14 to monitor progress of the infant.

10.2 Instructions for completing the Safety Monitoring Form (SUPP05)

The purpose of this form is to record daily information for the infant on ventilator strategy. Data will be recorded daily for all infants starting on Study Day 1 through Study Day 14. Study Day 1 is the day of randomization and information recorded for the study day is based on the calendar day and 24 hour clock. **A form will be filled out for each study day while infant is in the network hospital. Note: If more than one intubation/extubation occurs in one day, complete the supplemental SUPPO5A form.**

1. Study Day Enter the day this form is being completed.
2. Date: Enter the date that corresponds to the Study Day.

10.2.1 Section A. Blood Gas Information

Complete Section A If infant Intubated/CPAP for > 8 hours on this day.
All questions in this section pertain to the results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59. Record the blood gas **results closest to the scheduled time if available.** In no blood gases were measured, record the FiO_2 and the Mode of Support.

1. Scheduled Time: 08:00
2. Scheduled Time: 16:00
3. Scheduled Time: 23:59

a. Scheduled Time
The scheduled time is given on the first column of the table. Because a scheduled time is assigned to each of the 3 time points, scheduled times are labeled as 08:00, 16:00, and 23:59.

b. Time Measured
Record the time that the blood samples were collected based on a 24-hour clock. This time should be closest to 08:00, 16:00 or 23:59. If one blood gas qualifies as closest to two scheduled times (e.g. 23:59 and 8:00am the next day) enter the blood gas on the earlier of the selected times and enter ** : ** for the later one.

Record the results of the blood draw: If **No** blood gases were measured, record the time of the FiO_2 and the mode of support, leave questions c, d, e and g blank.

c. pH
Record the acid base status of the blood.
d. $C0_2$
e. PO_2:

f. FiO_2
Record the **FiO_2**measured.
g. **Source:**
Record the source of the blood draw
1= Arterial
2= Venous
3= Capillary

h. Mode of Support
Record the respiratory support as:
1 = HFV
2= CV
3 = Nasal SIMV
4 = CPAP
5= NC
6= Hood
7= No Support

4. If Mode of Support is CPAP, type used:
Record the type of CPAP used as:
2= Ventilator
4= Bubble
6= Flow Driver
9 = Other
If Other (9) specify type used

10.2.2 Section B. Supplemental Oxygen Information

Complete Section B If the infant is on Cannula/Hood for >8 hours on this day. The FiO_2 should be recorded once a day closest to Noon.

1. Scheduled Time: 12:00 (Noon)

a. Scheduled Time
The scheduled time is given on the first column of the table. Because a scheduled time is assigned the scheduled time is labeled as 12:00 (Noon).

b. Time Measured
Record the time that the ventilator settings were recorded based on a 24-hour clock. This time should be closest to12:00 (Noon).
c. FiO_2
Record the **FiO_2**.
d. Flow Rate
Record the flow rate.
e. Mode of O2 Delivery
Record the mode of O2 delivery
5 = Cannula
6= Hood

10.2.3 Section C. Intubation/Extubation Information (For NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form.

Record the intubation/extubation history for each Study Day 1- 14.

1. Was the infant intubated on this day?

Record Yes if the infant was intubated on this day.

a. If Yes, Record the time of intubation:

b. Record the following prior to intubation:

1. **pH**
2. **PCO_2**
3. **FiO_2**
4. **Saturation**
5. **Apnea?** Record Yes if the infant had Apnea on this day.
6. **Sepsis/R/O Sepsis?** Record Yes if the infant had Sepsis/R./O Sepsis on this day.
7. **Hemodynamic instability?** Record Yes if the infant had hemodynamic instability on this day.
8. **Clinically significant PDA?** Record Yes if the infant had clinically significant PDA on this day.
9. **Other (specify).** Record Yes if the infant had other conditions this day. Specify these.

2. Was the infant extubated on this day? Record Yes if the infant was extubated on this day.

a. If Yes, Record the time of intubation:

b. Type of extubation:
   1= Planned
   2= Accidental

c. Record the following prior to extubation:
   1. **pH**
   2. **PCO_2**
   3. **FiO_2**

3. Was a replacement study oximeter placed on this infant on this day?

If Yes,

a. Serial number: Enter the serial number of the replacement oximeter.

Chapter 11

Protocol Deviation Form

11. 1 Introduction

The purpose of the protocol deviation form is to facilitate the accurate documentation of the facts and circumstances surrounding a deviation from or violation of the protocol. This form should be completed for all randomized patients whenever a protocol deviation is encountered by study personnel. ***This form will be keyed at the sites.***

All protocol violations will be reviewed by the center PI who will discuss each protocol violation with the involved clinicians and provide a written summary including steps taken to avoid future violations.

11.2 Instructions for completing the Protocol Violation Report (SUPP06)

1. Date of Protocol Deviation:
Record the date the deviation was first encountered using the mm/dd/yyyy format.

2. Type of Protocol Deviation:
Record the type of protocol deviation:
1= Infant intubated without meeting study criteria
2= CPAP not initiated if required by the protocol
3= Surfactant not given in the first hour
4= Mechanical ventilation initiated for other than study criteria
5= NSIMV initiated in infant not previously intubated
6= Extubation (exclude unplanned extubation) for other than study criteria
7= Failure to extubate CPAP infant if all criteria are met
8= Infant received incorrect treatment assignment
If protocol deviation =8, indicate the treatment arm.
1= Ventilator strategy
2= Oximetry strategy
3= Both
9= Oximeter not started within 2 hours.
10= Other: Specify type of protocol deviation

3. Circumstances of the protocol deviation/violation:
Briefly describe the circumstances that led to the protocol deviation/violation. In particular, if there were medical reasons for deviating from/violating the protocol, describe them.

4. Additional comments:
Record any additional comments or information here such as steps taken to prevent recurrence of the deviation/violation.

5. Name of the person reporting the deviation/violation:
The name of the individual making the report should be recorded here.

6. Date Protocol Deviation Form is completed:
Record the date this form was completed.

Chapter 12

Reintubation Form

12.1 Introduction

The purpose of this form is to document all reintubations after day 14 for the duration of hospital stay.

12.1.1 Instructions for completing the Reintubation Form (SUPP07)

Complete this form for every reintubation and subsequent extubation after 14 days for the duration of hospital stay until status.

a. Event
Enter event code as:
1= Reintubation
2= Extubation

b. Date of event:
Enter the date of the event using the mm/dd/yyyy format.

c. Reasons for reintubation:
1 = Apnea / hypoventilation
2 = Increased respiratory effort
3 = Sepsis/Possible sepsis
4 = Atelectasis
5 = Elective procedures
6 = Upper airway abnormality
7= Self/Unplanned
8 = Other reasons

Record the code(s) corresponding to the reason(s) for the reintubation as recorded from the chart. There may be a maximum of three reasons recorded.

If code =8 other reasons, specify reason for reintubation if it is not listed.

d. Record FiO_2 and PCO_2 if available:
Record the FiO_2 and PCO_2, if within 6 hours prior to the event.

Chapter 13

Serious Adverse Experience

13.1 Introduction

Serious and unanticipated adverse events may be anticipated in this vulnerable population. **Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:**

1. Did the infant have any adverse events during the first 14 days of life?
If Yes, complete the Adverse Event Form and enter the Report Number in the header.

13.2 Adverse Event FORM (SUPP08)

Complete this for any randomized infant who experienced one or more of the following adverse events during the initial 14 days of life or prior to study status. This form should be completed and keyed at the sites as soon as possible.

1. Air leak in the first 14 days
2. The need for chest compressions, and/or epinephrine in the delivery room
3. The occurrence of severe IVH (Grades 3-4, Papile)[i]
4. Pulmonary Hemorrhage
5. Nasal breakdown requiring discontinuation of nasal prongs
6. Death
7. Other (specify) Specify if there were other adverse events.

13.3 Definition of a Serious Adverse Experience

1. An adverse experience is any undesirable experience associated with the use of a medical product in a patient.
2. Associated means that there is a reasonable possibility that the experience may have been caused by the drug.
3. Serious adverse experience means any experience that suggests a significant hazard, contraindication, side effect or precaution.
4. With respect to human clinical experience, a serious adverse drug experience includes any experience that is fatal or life threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

Death
Submit a report if the patient's death is suspected as being a direct outcome of the adverse event.

Life Threatening
Submit a report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death. Examples are: pacemaker failure; gastrointestinal hemorrhage; bone marrow suppression; infusion pump failure which permits uncontrolled free flow, resulting in excessive drug dosing.

Inpatient Hospitalization (initial or prolonged)
Submit a report if admission to the hospital or prolongation of a hospital stay results because of an adverse event. Examples are: anaphylaxis, pseudomembranous colitis, or bleeding causing or prolonging hospitalization.

Disability
Submit a report if the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life. Examples are: cerebrovascular accident due to drug-induced hypercoagulability, toxicity, peripheral neuropathy.

Requires Intervention to Prevent Permanent Impairment or Damage
Submit a report if you suspect that the use of a medical product may result in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient. Examples are: acetaminophen overdose-induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage, burns from radiation equipment requiring drug therapy, breakage of a screw requiring replacement of hardware to prevent malunion of a fractured long bone.

Adverse experiences will be reviewed by the Data Safety and Monitoring Committee.

13.4 Completing the MedWatch Form (SUPPO8A)

In the event of a patient death or unexpected serious adverse event not documented in the case report form, the PI must be notified right away. The attending physician should write a detailed description of the clinical events to include all the elements of the FDA 3500A (MedWatch) form (see Appendix **A**), the patient's date of birth, Network number, and whether the treatment was stopped. The description should be faxed to Dr. Rosemary Higgins at NICHD (301 496-3790) with a copy sent to Betty Hastings at the DCC (919 485-7762).

Chapter 14

Outcome Status Form

14.1 Introduction

The purpose of this form is to document the final outcome status of the infant.

14.1.1 Instructions for completing the Outcome Status Form (SUPP09)

This form is to be completed when the infant is discharged to home, transferred, if hospitalized at 120 days or death (which ever comes first).

14.1.2 Section A - Infant Outcome

1. **Status of infant at time of completion of form:**

   - **Discharged to home**
     Record '1' if infant was discharged to home without returning in 7 days.
   - **Still in hospital at 120 days**
     Record '2' if infant is still in the hospital at 120 days.
   - **Transferred to another hospital**
     Record '3' if infant was transferred to another hospital without returning in 7 days.
   - **Transferred to chronic care facility**
     Record '4' if infant was transferred to a chronic care facility without returning in 7 days.
   - **Death**
     Record '5' if the infant died.

2. **Date of status:**
   Give date at status.

14.1.3 Section B - Neurologic

1. **Did the infant have a head ultrasound between 4 - 21 days of age?**
   Code Yes if an ultrasound was performed between 4 - 21 days. Code No otherwise. If a cranial ultrasound is not done for standard of care, the study requires that at least one HUS be completed during this window.

If Yes,

a. Date of ultrasound:

Record the date of the head ultrasound obtained using the mm/dd/yyyy format. **Note**: If more than one head ultrasound is done between 4 - 21 days of age, record the date of the most severe.

If Yes,

b. Time of ultrasound:

Enter the time of the head ultrasound obtained using the 24 hour clock format (00:00-23:59).

c. Infarct?

Code Yes if an infarct was diagnosed by the local sonographer. Code No otherwise.

d. IVH?

Code Yes if evidence of intraventricular hemorrhage was observed on the head ultrasound. Code No otherwise.

If Yes,

1) IVH Grade:

Enter the severity of the intraventricular hemorrhage observed on the head ultrasound using the Papile scale:

Grade I: Code 1 if the echodensity/hemorrhage is confined to the germinal matrix/subependymal area.

Grade II: Code 2 if there is an echodensity/hemorrhage in the lateral ventricle(s) without distention.

Grade III: Code 3 if there is an echodensity/hemorrhage in the lateral ventricle(s) with distention.

Grade IV: Code 4 if there is an echodense lesion in the parenchyma.

e. PVL?

Code Yes if periventricular leukomalacia (increased echogenicity or cysts in periventricular region) was observed on the head ultrasound. Code No otherwise.

14.1.4 Section C – Ophthalmology

1. **Was an exam performed for Retinopathy of Prematurity (ROP)?**
   Review the medical record to determine if an examination was performed for ROP. **If Yes,** complete the **SUPP10 Form** (ROP Outcomes And Tracking Summary).

14.1.5 Section D – Postnatal Steroid Use

1. Did the infant receive postnatal steroids after the first 21 days of life?
If Yes, record the information on number of courses, start date, stop date, drug administered and total dose administered during the course in mg/kg. If No, the boxes are left blank.
Note: Only steroids given IV or PO are included for the purposes of this study. Inhaled steroids **are not** included.

a. Course:
A course is defined as all of the doses given in a period between an initial, usually high dose, and subsequent tapers. It may include a period when drug is given every other day. For the purposes of this study, a course is defined as ended when 72 hours passes without a steroid dose. If 72.5 hours passes and the infant receives another series of doses of the same or a different steroid, this is considered to be a second course.

b-c. Start and Stop Date:
The first and last doses given in a single course. RTI will use these dates to define the duration of exposure in days.

d. Drug:
Record the steroid administered using the following codes:
1= Dexamethasone
2= Betamethasone
3= Hydrocortisone
4= Prednisone
5= Other (Specify the other drug that was given)

e. Total Dose:
Calculate the total dose given in the course expressed as mg/kg. For example, the baby receives a course of dexamethasone beginning at 0.2 mg/kg for 2 days, and subsequent doses given as 0.1 mg/kg given for 2 days, 0.05 mg/kg for 2 days, 0.05 every other day for 2 doses, and then discontinue. The total dose administered to this patient is 0.2+0.2+0.1+0.1+0.05+0.05+0.05+0.05. The total dose administered is 0.8 mg/kg.

If the dose is not expressed in mg/kg in the medical record, the researcher calculates the mg/kg dose using: 1) the weight used in calculating the dose if documented, 2) the weight on the day the order was written to calculate the mg/kg.

Chapter 15

ROP Outcomes and Tracking Summary

15.1 Introduction

The purpose of this form is to track and document the acute ROP outcome of each eye. Tracking the course of ROP should begin with the first examination and will generally be much easier if the coordinator attends the examinations and asks the ophthalmologist in person about the categories to be recorded.

Data may be entered in the database from the form after each examination, or may be entered when the infant reaches "acute/final" status. However, monitoring of the examinations and progress will be much more complete and helpful if these are entered after each examination.

15.1.1 Instructions for completing the ROP Outcomes and tracking Summary (SUPP10)

Complete this form for all enrollees in SUPPORT who survive to have their first eye examination. This normally is scheduled at 31 weeks postmenstrual age (but not earlier than 4 weeks after birth).

Record the data for each eye examination until each eye has reached "acute/final" status (see definition below in 15.2). This will sometimes include examinations following discharge home or transfer to another hospital.

1. Date of Exam

If a confirming examination is conducted, each should be separately recorded.

2. Location of Exam

Code 1= inpatient for the primary hospital where the infant has been cared for, including other Units in that same hospital (step down units, pediatric intensive care, surgical care units, etc.)

Code 2=Outpatient for examinations in the outpatient ophthalmology department, private ophthalmologist's office or other outpatient visits. Include infants at a chronic care facility transported to the physician's office for an examination.

Code 3= Transfer Hospital when infants have been back transferred to a referring hospital or regional hospital.

Note: Outpatient and back transfer hospitals can be a common source of infants missing examinations and "slipping through the cracks". Be particularly attentive to ensuring timely repeat examinations in these cases and ensure that the family is aware of the importance and critical timing of the examinations.

3. **Lowest zone:** Record the lowest zone that contains vessels that end before crossing out of that zone. This may be zone I (the most immature), zone II (intermediate) or zone III (most mature). The ophthalmologist normally records this on the eye examination form. The most common for SUPPORT infants will be zone II at the early examinations. There may be vessels recorded in:
   - zone I and II (you record zone I)
   - zone I only (you record zone I)
   - zone II only (you record zone II)
   - zone III only (you record zone III)

   Note that by convention, disease is never to be recorded in zones II and III in the same eye. If the two nasal clock-hours are not fully vascularized, by convention, no vessels in that eye are to be recorded in zone III. If they are fully vascularized, the all the rest of that eye's vessels are in zone III.

4. **Highest stage in lowest zone** (not to be used if eye has had surgery)
   Look first at the lowest zone that has vessels ending in it (see previous answer). Then look to see if there is ROP in any of the clock hours of that zone. Choose the highest stage of ROP in that zone to record.

   Examples:
   If the eye has vessels ending in just zone I, but no ROP, the highest stage is zero.

   If the eye has vessels ending in zone I and zone II and the ROP in zone I is stage 2 while the ROP in zone II is stage 3, the highest stage in the lowest zone (I) is stage 2.

   If the eye has vessels ending in zone I, but there is no ROP in zone I, but there is stage 2 and stage 3 ROP in zone II, the answer would be 0=no ROP in the lowest zone.

5. **Highest stage in any zone** (not to be used if eye has had surgery)
   Look at the stage of ROP around the 12 clock-hours of the recorded examination. Choose the highest stage to record. In rank order going from lowest to highest the order is 0, 1, 2, 3, 4a, 4b, 5. The other categories are for less common cases.
   - Code 4 = stage 4a is a partial retinal detachment, not involving the macula
   - Code 5 = stage 4b is a partial retinal detachment that does involve the macula
   - Code 6 = stage 5 which is a total retinal detachment
   - Code 7 is used for eyes that have already been treated with laser or cryo
   - Code 8 = an eye that is recovering but shows old scars

6. **"Plus disease"**
   This is recorded by the ophthalmologist as present or not. Sometimes they provide comments like 'borderline plus' or 'possible early plus disease' or 'mild dilation, but not plus disease'. In these cases, do not record 'plus disease' as present. If the ophthalmologist records plus disease by quadrants, two or more quadrants are required to meet criteria for plus disease (i.e. only one quadrant of dilated/tortuous vessels is not sufficient.).

7. Threshold (New Type 1 threshold per ETROP)

The ophthalmologist who diagnoses threshold ROP needing surgery will normally state this prominently on the examination form. The criteria for the new threshold are any of the following four findings:

If in zone I: stage 3 ROP, even without plus disease
plus disease with any stage ROP

If in zone II: plus disease with stage 2 ROP
plus disease with stage 3 ROP

There may be times when disease is worse than this, but it should still be recorded as threshold.

There will be some times when the judgment of the retinal surgeon and neonatologist will be not to administer treatment (laser or cryo), even when there is new threshold. Normally infants are then followed extremely closely (every few days repeat examinations).

8. Surgery

For each examination date, record if surgery is performed on that day. (mostly will be no). If surgery was previously performed, but not on the day of that examination, record 0

9. Post-surgical Retinal Detachment after surgery

This at first looks like a repeat of the question asking for stage of ROP, but it is not since it is intended to be used only after surgery has occurred.

15.2 Acute/final Status

An eye is 'acute/final" when it reaches one of the following points in time:
These can be a good outcome (favorable) as the ROP heals (regresses), or it can be the primary outcome variable event (unfavorable).

- Favorable
  1 = Vessel growth if mature to the ora serrata in all clock hours
  2 = Vessels in zone III for two sequential eye examinations
  (i.e. two examinations in a row)

- Unfavorable
  3 = type I threshold ROP
  4 = Laser (or cryo or both) surgery for acute ROP
  5 = retinal detachment stage 5
  6 = retinal detachment stage 4b

- Other
  7 = Infant dies.

Chapter 16

Respiratory Support after 14 Days

16.1 Introduction

The purpose of this form is to document any respiratory support the infant receives after day 14.

16.1.1 Instructions for completing the Respiratory Support Form after 14 Days (SUPP11)

This form is only to be completed if the infant in on support after day 14. Do not complete this form if the infant is on "No support" or R/A cannula at <500cc. List the highest level of support which the infant was on for **more than 4 hours.**

Record the following for each day of support:

- Date
- Highest FiO2,
- Highest Level of Support (Only consider support which the infant was on for at least 4 hours.
- Cannula flow rate **Note:** For purposes of this form, a room air nasal cannula should be considered support only if it is > 500cc/min.

APPENDIX A

STUDY FORMS

SUPP01	**Screening Log**
SUPP02	**Eligibility Form**
SUPP03	**Delivery Form**
SUPP04	**NICU Admission Form**
SUPP05	**Safety Monitoring Form**
SUPP06	**Protocol Deviation Form**
SUPP07	**Reintubation Form**
SUPP08	**Adverse Event Form**
SUPP08A	**MedWatch Form**
SUPP09	**Outcome Status Form**
SUPP10	**ROP Outcomes and Tracking Summary**
SUPP11	**Respiratory Support After 14 Days**

APPENDIX B

SAMPLE CONSENT FORM

University of California, San Diego
Consent to Act as a Research Subject

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial of the NICHD Neonatal Research Network

Neil Finer, MD, his associates, and the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network are conducting a research study to find out more about treatment with CPAP (positive pressure applied with a face mask to help keep the lungs inflated) and learn the appropriate levels of oxygen saturation (oxygen levels in the blood) in premature babies. You are being asked to allow your child to be in the study because there is a possibility he/she will be born between 16 and 12 weeks early (24-28 weeks gestational age).

The purposes of this trial are the following:
1) To compare infants who receive delivery room CPAP and who have strict guidelines for having a breathing tube placed with infants who have the tube placed and surfactant (a liquid which helps babies with immature lungs breath easier by helping keep their lungs from collapsing) given in the delivery room.
2) To compare low range (85-89%) oxygen saturation levels with high range (91-95%) levels to determine if a lower range results in decreased ROP (Retinopathy of Prematurity, an eye disease that may result in impairment of vision or even blindness, which may be caused by excessive levels of oxygen.)

Duration of the Study: We expect to include about 1300 babies in the study from all the NICHD Neonatal Research Network hospitals over a two year period.

The use of CPAP and Intubation/Surfactant are both treatments currently used in the delivery room at UCSD. The decision as to which to use is currently made by the physician attending the delivery.

The oxygen level currently used in the NICU at UCSD is between 85% and 95%. Both treatment groups (85-89% and 91-95%) fall within that range. The study will attempt to keep babies in one of these two smaller ranges.

If you agree to allow your child to be in this study, the following will happen to your child:
Prior to delivery, and after your permission, your baby will be randomized (chosen by chance like the flip of a coin) to one of two lung treatment strategies. The treatments are as follows:
1) CPAP in the delivery room immediately after birth and continuing in the NICU, or
2) The placement of a tube in his/her trachea (windpipe) in the delivery room followed by surfactant administration and ventilation (breathing for the baby using a machine).

In addition to being randomly assigned to one of the two groups described above, your baby will be randomized to a High reading or Low reading oximeter (a monitor that displays how much oxygen is in the blood). The oximeters (oxygen monitors) used in this trial are FDA approved oximeters which have been modified for research purposes. This modification makes the monitors show a value which is either slightly higher or slightly lower than the true oxygen level when values are between 85 and 95%. Outside those ranges, the oximeter works the same as the standard of care device.

Which group your baby is randomized to will not be known to the nurse taking care of your baby, or his/her physician. Only the study coordinator will know which group your baby is in. Within the range of oxygen which we normally keep babies in, your baby will either be on the high end of normal or the low end of normal. He/she will remain on this device until he/she reaches 36 weeks adjusted age. (e. g. 24 wks gestation plus 12 weeks of age = 36 weeks adjusted age). Other care will be conducted as normal during his/her participation in the study. Your baby will be followed in our Infant Follow-up clinic at 6 and 12 months as standard of care for small babies. At 18-22 months corrected age your baby will receive, at no charge to you, a complete exam of their muscles, nerves, and mental and coordinated movement skills.

Participation in this study may involve some added risks or discomforts. Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby. Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted ventilation (methods to help them breathe). If the attending physician deems this necessary, participation in the study will not affect this decision. Some unknown risks may be learned during the study. If these occur, you will be informed by the study personnel. The only other risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential. There will be no name or other patient identification in any study report that may be published after the study is completed. Measures taken to protect you and your baby's identity are described in the confidentiality section of this document.

There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen near discharge) and/or a decrease in the need for eye surgery as a result of exposure to oxygen. Because we do not know in advance the actual strategies chosen for your child, or which of the treatment strategies is the most effective, it is also possible that your baby will receive no direct benefit. The knowledge learned from this study may help us treat babies in the future. However, as noted above, each of the 4 possible combinations of treatments is considered by some units to represent their desired approach.

If your child is injured as a direct result of participation in this research, the University of California will provide any medical care your child needs to treat those injuries. The University will not provide any other form of compensation to you if your child is injured. You may call the UCSD Human Research Protections Program office at (858) 455-5050 for more information about this, or to inquire about your rights as a research subject, or to report research-related problems.

_____ has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Wade Rich, the Study Coordinator, or Renee Bridge, the Research Nurse, at 619-543-6560. You may contact the principal investigator Dr. Neil Finer at 619-543-3794

As an alternative to participation in this study you may decide to have your baby's doctor decide which treatment your baby will receive. If you decide not to include your child in this study, none of his/her medical information will be included in the study data. Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care your child will receive at this institution of other loss of benefits to which your child is entitled. If you withdraw your child from the study, the attending physician will decide whether to maintain current treatment or change it, based on your child's needs at the time of the decision. Data collection for research purposes will stop at that time.

Clinical information will be collected from your baby's chart by study personnel at UCSD. Information will be labeled with a code number. Coded information will be sent to the NICHD Neonatal Network's Data Collection Center at Research Triangle Institute (RTI) in Research Triangle Park, North Carolina. The study log linking the code number with your baby's identity will be kept under lock and key at UCSD. Information directly identifying your baby will not leave UCSD. Research records will be kept confidential to the extent provided by law.

You may withdraw your child from the study for any reason. In addition, the study doctors may decide to withdraw your child if they feel it is in his/her best interest to do so.

You have received a copy of this consent document to keep and the Experimental Subject's Bill of Rights

You agree to have your child participate.

_____

Parent's or legal guardian's signature DATE

_____

Relationship of legal guardian to subject DATE

_____

Signature of person explaining and getting consent DATE

APPENDIX C

PHYSIOLOGIC DEFINITION OF BRONCHOPULMONARY DYSPLASIA (Refer to Stand Alone Protocol, Manual of Operations and Forms)

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: ___ Site No: ___ Network No: ___ Birth No: ___ Mother's Initials: ___

1. Study Day: ___ (This form is only completed if the infant is on support after day 14. Do not fill out if on no support or R/A cannula at <500cc.)

LIST THE HIGHEST LEVEL OF SUPPORT WHICH THE INFANT WAS ON FOR MORE THAN 4 HOURS.

(a) DAY OF SUPPORT	___	___	___	___	___	___
(b) Date	___/___/___ Month Day Year	___/___/___ Month Day Year	___/___/___ Month Day Year	___/___/___ Month Day Year	___/___/___ Month Day Year	___/___/___ Month Day Year
(c). Highest Level of Support	___	___	___	___	___	___
(d) FiO_2 Most Frequent during (c). If two are equal, choose highest.	___.___	___.___	___.___	___.___	___.___	___.___
(e) Flow Rate	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(a) DAY OF SUPPORT	___	___	___	___	___	___
(b) Date	___/___/___ Month Day Year	___/___/___ Month Day Year	___/___/___ Month Day Year	___/___/___ Month Day Year	___/___/___ Month Day Year	___/___/___ Month Day Year
(c) Highest Level of Support	___	___	___	___	___	___
(d) FiO_2 Most Frequent during (c) If two are equal, choose highest.	___.___	___.___	___.___	___.___	___.___	___.___
(e) Flow Rate	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(a) DAY OF SUPPORT	___	___	___	___	___	___
(b) Date	___/___/___ Month Day Year	___/___/___ Month Day Year	___/___/___ Month Day Year	___/___/___ Month Day Year	___/___/___ Month Day Year	___/___/___ Month Day Year
(c) Highest Level of Support	___	___	___	___	___	___
(d) FiO_2 Most Frequent during (c) If two are equal, choose highest.	___.___	___.___	___.___	___.___	___.___	___.___
(e) Flow Rate	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.

1= HFV 2= CV 3= Nasal SIMV 4= CPAP * 5= NC 6=Hood

*** NOTE: NASAL CANNULA IN ROOM AIR IS ONLY CONSIDERED A LEVEL OF SUPPORT AT FLOW RATES >500cc/min.**

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Screening Log

Center: ___ ___ **Site:** ___

Mothers deemed to be at risk of premature delivery at 27 6/7 weeks or less should be entered on this form

< This section to be filled out when potential infant identified > <This section to be filled out when the infant is born>

Mother's Last Name	Mother's Hospital Number	Gestational Age (wks/days)	Last Date Eligible (Month/Day/Year)	Consent (Y/N)	Date of Birth (Month/Day/Year)	Enrolled in study Y/N	Network Number	Birth No.	Comments
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	
		__ __ __	__/__/____	__	__/__/____	__	_____	__	

<

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SUPP02 Rel 1.0
January 4, 2005

Eligibility Form

Center: ___ Site: ___ Network No. ____ Birth No. __ Mother's Initials: ___

This form should be completed for all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation.

A. INCLUSION CRITERIA

1. Inborn infant with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimate? Y N
2. Infant to receive full resuscitation as necessary? Y N
3. Infant does not have known major congenital malformations? Y N

If any of above questions are answered 'N' infant is NOT eligible.

B. EXCLUSION CRITERIA

1. The infant was born during a time when the research apparatus/study personnel are not available? Y N

   If Yes, indicate reason: ___

1= Equipment not available	2 = Personnel not available

C. CONSENT

1. Consent Status: ___

0 = Not eligible	**4** = Consent not requested
1 = Consent granted	**5** = Physician refused consent
2 = Parent unavailable	
3 = Parent refused consent	

a. If parent refused consent (3), consent not requested (4) or physician refused consent (5), indicate reason:

_____

_____

D. RANDOMIZATION

1. Was infant randomized into the study? Y N

   If **No**, indicate reason(s):_____

   If Yes,

   a. Date: __/__/__ __ __ __ (Month / Day / Year) b. Time: __:__ (Hour / Min)

   c. Randomization Number ____

   d. Treatment Assignment ___

1= Early Extubation and CPAP	2= Early Surfactant and Ventilation

   e. Oximeter Color Code: ___

1= Blue	2= Orange

Initials of person completing this form: ___

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants
Delivery Form

Center: __ __ Site: ___ Network No. __ __ __ __ Birth No. ___ Mother's Initials: __ __ __

A. DELIVERY ROOM INFORMATION

1. Date and time of delivery:

   a. Date: __ __/__ __/__ __ __ __ (Month Day Year) b. Time: __ __: __ __ (Hour Min)

2. Was CPAP initiated in the DR? Y N

   If Yes, Date and time of CPAP initiation:

   a. Date: __ __/__ __/__ __ __ __ (Month Day Year) b. Time: __ __: __ __ (Hour Min)

   c. Device: ___

1= Neopuff	2= Ventilator	3= Anesthesia Bag	4 = Bubble	9= Other

   If (5) Other (specify device) _____

3. Was positive pressure ventilation (PPV) initiated in the DR? Y N

4. Was positive end expiratory pressure (PEEP) used in the DR? Y N

   If Yes,

   a. Maximum PEEP: __ __

5. Was intubation attempted in the DR? Y N

   a. If Yes, was the intubation successful? Y N

6. Indication for Intubation: ___

1= Surfactant administration	2= Resuscitation	3= Other (specify)	4= As required by randomization assignment

   If (2) Resuscitation,

   a. Low HR? Y N

   b. Poor color? Y N

   c. Apnea? Y N

   d. Other (specify):_____ Y N

   If (3) Other (specify):_____

7. Did the infant receive surfactant in the DR? Y N

   If Yes, Date and time of administration:

   a. Date: __ __/__ __/__ __ __ __ (Month Day Year) b. Time: __ __: __ __ (Hour Min)

   c. Type: ___

1= Infasurf	2= Curosurf	3= Survanta	4= Exosurf	5= Other (Specify)

   If (5) Other (specify type) _____

8. Was active resuscitation required? Y N

   If Yes,

   a. Chest compressions? Y N

      If Yes,

      1. Duration: __ __ (Min)

   b. Epinephrine? Y N

      If Yes,

      1. Number of doses: __ __

9. Status following resuscitation: ___

1=Admitted to NICU for further care
2=Infant Died

Initials of person completing this form: __ __ __

NICU Admission and Procedures Form

Center: __ __ Site: __ Network No. __ __ __ __ Birth No. __ Mother's Initials: __ __ __

A. NICU ADMISSION

1. Date and time of NICU admission:

a. Date: __ __/__ __/__ __ __ __ (Month Day Year) b. Time: __ __: __ __ (Hour Min)

2. Respiratory Support on admission to the NICU: __

1= HVF	2= CV	3= Nasal SIMV	4=CPAP	5= NC	6= Hood	7= No Support

3. SaO_2 __ __ __

4. FiO_2: __ . __ __

5. Was a blood gas done after admission to the NICU? Y N

If yes, record the first blood gas after admission.

a. Date: __ __/__ __/__ __ __ __ (Month Day Year) b. Time: __ __: __ __ (Hour Min)

c. Source: __

1= Arterial	2= Venous	3= Capillary

d. pH __ . __ __

e. pCO_2 __ __ __

f. pO_2 __ __ __

g. FiO_2 __ . __ __

6. Date and time the study oximeter was placed on this infant.

a. Date: __ __/__ __/__ __ __ __ (Month Day Year) b. Time: __ __: __ __ (Hour Min)

c. Serial number: __ __ __ __ __ __ __

B. NICU PROCEDURES

1. Was the infant intubated for the first time within the first 14 days after admission to the NICU? Y N

If Yes,

a. Date: __ __/__ __/__ __ __ __ (Month Day Year) b. Time: __ __: __ __ (Hour Min)

c. Indication for intubation:

1. Surfactant? Y N
2. $FiO_2 > .50$ to maintain $SaO_2 \geq 88\%$? Y N
3. $pCO_2 > 65$ on single blood gas? Y N
4. Apnea requiring bag and mask ventilation? Y N
5. If No to all above, state reason: __

1= Hemodynamic instability	2 = Clinical shock/sepsis	3 = Other

If Other (3), specify______________________________

2. Was a blood gas done within 30 minutes prior to intubation? Y N

If Yes,

a. Date: __ __/__ __/__ __ __ __ (Month Day Year) b. Time: __ __: __ __ (Hour Min)

c. Source: __

1= Arterial	2= Venous	3= Capillary

d. pH __ . __ __

e. pCO2 __ __ __

f. pO2 __ __ __

g. FiO2 __ . __ __

3. Was Surfactant given in the NICU? Y N

If Yes,

a) Dose#	b) Date:	c) Time:	d) Type:*
1	__ __/__ __/__ __ __ __ (Month Day Year)	__ __: __ __ (Hour Min)	__
2	__ __/__ __/__ __ __ __ (Month Day Year)	__ __: __ __ (Hour Min)	__
3	__ __/__ __/__ __ __ __ (Month Day Year)	__ __: __ __ (Hour Min)	__
4	__ __/__ __/__ __ __ __ (Month Day Year)	__ __: __ __ (Hour Min)	__

*1= Infasurf	2= Curosurf	3= Survanta	4= Exosurf	5= Other (Specify)

If Other (5), specify______________________________

Initials of person completing this form: __ __ __

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SUPP05 Rel 2.0
March 10, 2005

SAFETY MONITORING FORM

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete a form each day starting with Study Day 1 until Study Day 14 or outcome status, whichever comes first. Note: Study Day 1 is the day of randomization and is based on the calendar day (00:00 - 23:59).

1. Study Day: __ __ **2. Date:** __ __ / __ __ / __ __ __ __

COMPLETE SECTION A IF THE INFANT IS INTUBATED/CPAP FOR > 8 HOURS ON THIS DAY (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If No blood gases were measured, enter FiO_2 and Respiratory Support.

(a) Scheduled Time	(b) Time Measured (hour : min)	(c) pH	(d) CO2	(e) PO2	(f) FIO_2	(g) Source*	(h) Mode** of Support
1. 8 : 00	__ __ : __ __	__ . __ __	__ __ __	__ __ __	__ . __ __	___	___
2. 16 : 00	__ __ : __ __	__ . __ __	__ __ __	__ __ __	__ . __ __	___	___
3. 23 : 59	__ __ : __ __	__ . __ __	__ __ __	__ __ __	__ . __ __	___	___

* 1= Arterial 2= Venous 3 = Capillary

** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

4. If Mode of Support is CPAP, type used: ___

2= Ventilator 4= Bubble 6 = Flow Driver 9= Other

If (9) Other specify type : _____

COMPLETE SECTION B IF INFANT IS ON CANNULA/HOOD FOR > 8 HOURS ON THIS DAY (RECORD FiO_2 ONCE A DAY CLOSEST TO NOON)

B. SUPPLEMENTAL OXYGEN INFORMATION: Record results closest to noon, if available.

(a) Scheduled Time	(b) Time Measured (hour : min)	(c) FiO_2	(d) Flow Rate	(e) Mode of O2 Delivery
1. 12 : 00 (Noon)	__ __ : __ __	__ . __ __	__ . __ __ __	___

** 5= Cannula 6= Hood

C. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete the SUPP05A Form

1. Was the Infant intubated on this day? Y N

a. If Yes, Record the time of intubation __ __ : __ __ (Hr : Min)

b. Record the following prior to intubation :

1. pH __ . __ __
2. PCO_2 __ __ __
3. FiO_2 __ . __ __
4. Saturation __ __ __
5. Apnea? Y N
6. Sepsis/R/O Sepsis? Y N
7. Hemodynamic instability? Y N
8. Clinically significant PDA? Y N
9. Other (specify)? _____ Y N

2. Was the Infant extubated on this day? Y N

a. If Yes, Record the time of extubation __ __ : __ __ (Hr : Min)

b. Type of extubation: ___

1= Planned 2= Accidental

c. Record the following prior to extubation

1. pH __ . __ __
2. PCO_2 __ __ __
3. FiO_2 __ . __ __
4. Saturation __ __ __

3. Was a replacement study oximeter placed on this infant on this day? Y N

If Yes,

a. Serial number: __ __ __ __ __ __

Initials of person completing this form: __ __ __

PROTOCOL DEVIATION FORM

Center: __ __ Site No: ___ Network No. __ __ __ __ Birth No: ___ Mother's Initials: __ __ __ Report No: __

This form should be completed for all randomized patients whenever a protocol deviation is encountered by study personnel. This form will be keyed at the sites.

1. **Date of Protocol Deviation:** __ __ / __ __ / __ __ __ __ (Month / Day / Year)

2. **Type of protocol deviation:**

   1. **Infant intubated without meeting study criteria.**
   2. **CPAP not initiated if required by protocol.**
   3. **Surfactant not given in the first hour.**
   4. **Mechanical ventilation initiated for other than study criteria.**
   5. **NSIMV initiated in infant not previously intubated.**
   6. **Extubation (exclude unplanned extubation) for other than study criteria?**
   7. **Failure to extubate CPAP infant if all criteria met.**
   8. **Infant received incorrect treatment assignment.**

   If protocol deviation =8, indicate treatment arm ___

1= Ventilator Strategy	2= Oximetry Strategy	3= Both

   9. **Oximeter not started within 2 hours.**
   10. **Other? *(Specify)*** _____

3. **Circumstances of the Protocol Deviation:**

   _____

   _____

   _____

4. **Additional Comments:**

   _____

   _____

   _____

5. **Name of Person who reported the protocol deviation on this form:**

   _____

6. **Date Protocol Deviation Form is completed:** __ __ / __ __ / __ __ __ __ (Month / Day / Year)

   Initials of person completing this form: __ __ __

The Surfactant, Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Reintubation Form

Center: ___ Site: ___ Network No. ____ Birth No. ___ Mother's Initials: ___

Complete this form for all Intubations/ extubations after 14 days.

a. Event 1= Reintubation 2= Extubation	b. Date Month / Day / Year	c. Reasons for Reintubation:* a. code 1 b. code 2 c. code 3	d) Record FiO_2 and PCO_2 if available: Provide if within 6 hours prior to the event	
			FiO_2	PCO_2
1. ___	__/__/____	___ ___ ___	_._ __	__
2. ___	__/__/____	___ ___ ___	_._ __	__
3. ___	__/__/____	___ ___ ___	_._ __	__
4. ___	__/__/____	___ ___ ___	_._ __	__
5. ___	__/__/____	___ ___ ___	_._ __	__
6. ___	__/__/____	___ ___ ___	_._ __	__
7. ___	__/__/____	___ ___ ___	_._ __	__
8. ___	__/__/____	___ ___ ___	_._ __	__
9. ___	__/__/____	___ ___ ___	_._ __	__
10. ___	__/__/____	___ ___ ___	_._ __	__
11. ___	__/__/____	___ ___ ___	_._ __	__
12. ___	__/__/____	___ ___ ___	_._ __	__
13. ___	__/__/____	___ ___ ___	_._ __	__
14. ___	__/__/____	___ ___ ___	_._ __	__
15. ___	__/__/____	___ ___ ___	_._ __	__

□*Reason codes for reintubation

1 =Apnea / hypoventilation

2 =Increased respiratory effort

3 =Sepsis/Possible sepsis

4 =Atelectasis

5 =Elective for procedures

6 =Upper airway abnormality

7 =Self/Unplanned

8 =Other reasons (Specify)

Complete this form for any randomized infant who experienced one or more of the following adverse events during the initial 14 days of life or prior to study status. This form will be keyed at the sites.

1. Did the infant have any adverse events during the first 14 days of life? Y N

If Yes,

ADVERSE EVENT	DATE Of ONSET (mm/dd/yyyy)	ATTRIBUTABLE TO SUPPORT STUDY 0 = No 1 = Not likely 2 = Possibly 3 = Probably	COMMENTS
1. Air leak in the first 14 days	__ __/__ __/__ __ __ __	___	
2. Need for chest compressions and/or epinephrine in the delivery room	__ __/__ __/__ __ __ __	___	
3. The occurrence of severe IVH (grades III-IV)	__ __/__ __/__ __ __ __	___	
4. Pulmonary Hemorrhage	__ __/__ __/__ __ __ __	___	
5. Nasal breakdown requiring discontinuation of nasal prongs		___	
6. Death	Date of Death __ __/__ __/__ __ __ __	___	
7. Other (Specify) _____ _____ _____	__ __/__ __/__ __ __ __	___	

Initials of Person Completing this Form: __ __ __

Center: ___ Site: ___ Network No. _____ Birth No. __ Mother's Initials: _____

Complete this form when the infant is discharged to home, transferred, if hospitalized at 120 days or death (whichever comes first).

A. INFANT OUTCOME

1. Status: _____

1 = Discharged home alive	4 = Transferred to a chronic care facility.
2 = Still in hospital at 120 Days	5 = Death
3 = Transferred to another hospital	

2. Date of Status: __ __/__ __/__ __ __ __ (Month / Day / Year)

B. NEUROLOGIC

1. Did infant have a head ultrasound between 4 - 21 days of age? Y N

If YES,

a. Date: __ __/__ __/__ __ __ __ (Month / Day / Year) b. Time: __ __ : __ __ (Hour / Min)

c. Infarct? Y N

d. IVH? Y N

If YES,

1) IVH Grade: ___

1 = I 2 = II 3 = III 4 = IV

e. PVL? Y N

C. OPHTHALMOLOGY

1. Was an exam performed for ROP? Y N

If YES, Complete the SUPP10 Form

D. POSTNATAL STERIOD USE

1. Did the infant receive postnatal steroids after the first 21 days of life? Y N

If YES,

(a) Course	(b) Start Date (Month/ Day/ Year)	(c) Stop Date (Month/ Day/ Year)	(d) *Drug	(e) Total Dose (mg/kg)
1	__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	___	__ __ . __
2	__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	___	__ __ . __
3	__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	___	__ __ . __
4	__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	___	__ __ . __
5	__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	___	__ __ . __

*Drug Codes	
1= Dexamethasone	4= Prednisone
2= Betamethasone	5= Other (Specify)_____
3= Hydrocortisone	

Initials of person completing this form: ___

The SUPPORT Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

ROP OUTCOMES AND TRACKING SUMMARY

Center: __ __ Site: ___ Network No. __ __ __ __ Birth No. ___ Mother's Initials: __ __ __

Record the data for each eye examination (in or outpatient) until both eyes are acute/final. Indicate when examinations switch from the NICU to a back-transfer hospital, or to outpatient

		Examination Results									Examination Results								
		Left Eye									Right Eye								
Date of Exam	`Location of Exam	Lowest* Zone of any Vessels	Highest+ Stage in lowest Zone	Highest+ Stage In any Zone	"Plus Disease"		Threshold (New Type 1)		Surgery^	Post-surgical Retinal** Detachment	Lowest* Zone of any Vessels	Highest+ Stage in lowest zone	Highest+ Stage In any Zone	"Plus Disease"		Threshold (New Type 1)		Surgery^	Post-surgical Retinal** Detachment
1. __ __/__ __/__ __ __ __	___	___	___	___	Y	N	Y	N	___	___	___	___	___	Y	N	Y	N	___	___
2. __ __/__ __/__ __ __ __	___	___	___	___	Y	N	Y	N	___	___	___	___	___	Y	N	Y	N	___	___
3. __ __/__ __/__ __ __ __	___	___	___	___	Y	N	Y	N	___	___	___	___	___	Y	N	Y	N	___	___
4. __ __/__ __/__ __ __ __	___	___	___	___	Y	N	Y	N	___	___	___	___	___	Y	N	Y	N	___	___
5. __ __/__ __/__ __ __ __	___	___	___	___	Y	N	Y	N	___	___	___	___	___	Y	N	Y	N	___	___
6. __ __/__ __/__ __ __ __	___	___	___	___	Y	N	Y	N	___	___	___	___	___	Y	N	Y	N	___	___
7. __ __/__ __/__ __ __ __	___	___	___	___	Y	N	Y	N	___	___	___	___	___	Y	N	Y	N	___	___
8. __ __/__ __/__ __ __ __	___	___	___	___	Y	N	Y	N	___	___	___	___	___	Y	N	Y	N	___	___
9. __ __/__ __/__ __ __ __	___	___	___	___	Y	N	Y	N	___	___	___	___	___	Y	N	Y	N	___	___
10. __ __/__ __/__ __ __ __	___	___	___	___	Y	N	Y	N	___	___	___	___	___	Y	N	Y	N	___	___

`LOCATION:	1= Inpatient	2 = Outpatient	3= Transfer Hospital

*ZONE:	1= I	2 = II	3= III	4 = Mature	5= Status post laser/cryo	9=Unable to determine

+ STAGE:	0= No ROP	1= Stage 1	2=Stage 2	3= Stage 3	4= Stage 4a or 4b	5= Stage 5	6= Post laser/cryo (do not use stages)	9 = Old scars, but no active ROP

^ SURGERY:	0= No surgery this day	1= Laser	2= Cryotherapy	3= Both laser/cryo	4=Scleral buckle	5= Vitrectomy	6= Other

**RETINAL DETACHMENT:	0= None	3= Partial, not involving macula (stage 4a)	4 = Partial, does involve macula (stage 4b)	5 = Complete	9=View obscured, can't tell

From: Stevens, Timothy
To: Higgins, Rosemary (NIH/NICHD) [E]; "nfiner@ucsd.edu"; Phelps, Dale
Subject: Budget Pulmonary Outcomes for Support
Date: Thursday, June 09, 2005 9:25:34 PM
Attachments: Letter to Rose.doc
Costs for Follow-on.xls

Hi Rose,

Attached is the revised budget. A cover letter is also attached.

Let me know if I can do anything,

Thanks

Tim

-----Original Message-----
From: Stevens, Timothy
Sent: Wednesday, June 08, 2005 8:54 PM
To: 'Higgins, Rosemary (NIH/NICHD)'; 'nfiner@ucsd.edu'; Phelps, Dale
Subject: RE: Pulmonary Outcomes for Support

Hi Rose,

I'm meeting with Dale tomorrow to review and update the budget for the Pulmonary Outcomes follow on study. The budget to the NICHD will depend on whether my K23 is funded. Dr. Raju said that I am likely just above the payline at NICHD. Fortunately, I asked for a dual assignment with NHLBI. I understand that my K23 is under consideration through that institute. It would be nice to pull in NHLBI funding to help support the Pulmonary Outcomes Study. Do you know when the NHLBI funding decision will be available?

Thanks

Tim Stevens

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, May 31, 2005 7:55 AM
To: Stevens, Timothy
Cc: Phelps, Dale
Subject: FW: Pulmonary Outcomes for Support

Tim
Here are a few more suggestions from Roy for the pulmonary outcomes protocol. I think we need to work on a new budget - one that considers the sites doing the questionnaires - probably will take 2-3 hrs/per group. Can you do this?
Thanks
Rose

-----Original Message-----
From: Roy Heyne [mailto:Roy.Heyne@UTSouthwestern.edu]
Sent: Tuesday, May 31, 2005 8:47 AM

To: Higgins, Rosemary (NIH/NICHD)
Cc: JANET MORGAN; BVohr@WIHRI.org
Subject: Fwd: Pulmonary Outcomes for Support

Janet just reminded me of two more points, which I did not include in my comments last Friday, though I did raise one at our meeting in D.C.: 1) We need to provide some incentive for participation, since this will involve additional time and trouble on the part of the family; 2) as in the case of the PCV7 study, we need the flexibility to be able to enroll and obtain the baseline questionnaire within 2-4 weeks after discharge (at our first follow-up visit), rather than prior to discharge, which latter is a more challenging time to try to connect with our families).

>>> Roy Heyne 05/27/05 5:41 PM >>>
One other interesting article that addresses the llimited accuracy of reported wheezing was published last year in Arch Dis Child 89:540-543 by Lowe et. al.

>>> Roy Heyne 05/27/05 4:05 PM >>>
Rose, I am attaching a Word document with my comments regarding the proposed SUPPORT pulmonary follow-on study. LEt me know if you have questions. Thanks for considering.

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 05/23/05 11:25 AM >>>
Janet
Thanks so much for getting back to us. I believe patient (b) (6) originated from the Cincinnati site. Is this correct?
Thanks again for the attention to the details!
Rose

-----Original Message-----
From: JANET MORGAN [mailto:JANET.MORGAN@childrens.com]
Sent: Monday, May 23, 2005 12:00 PM
To: Roy Heyne
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: Re: Fwd:

Dr. Heyne,
We have completed clients # (b) (6), info has not yet been entered. Clients (b) (6) are scheduled in May and June. Clients (b) (6) are for various reason not scheduled yet. Two of these are out of town and we are tring hard to get some follow-up..not sure we will be successful and the other we are having trouble locating.
Janet

>>> Roy Heyne 5/20/2005 11:35:48 AM >>>
Could you please check these out. Thanks.

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 05/20/05 11:22 AM >>>

Hi,

We appreciate the hard work and dedication of all the sites in their

participation in the Preemie iNO trial. As you know, a crucial component of this trial is neurodevelopmental outcome at 18-22 months corrected age. To assure the best possible follow-up, we ask you to look into the following follow-up issues, and respond to concerns as soon as possible. Please note that, even if the follow-up window has "closed", the neurodevelopmental follow-up visit should still be done.

Preemie iNO Surviving Infants Not Followed Up

Mother First Name	Mother Last Name	Follow-up Start Date	Follow-up End Date	Gestational Age Birth Weeks	Study Center Name	ID
					4:Univ. of Texas Dallas	(b) (6) (b) (6)
32	Main	PR	THO	07/10/04	11/23/04	
					(b) (6) (b) (6)	
31	Main	SMP	12/31/04	05/16/05		
					(b) (6) (b) (6)	
28	Main	AC	05/04/05	09/17/05		
					(b) (6)	
27	Main	LMV	05/19/05	10/02/05		
					(b) (6)	
32	Main	MR	04/19/05	09/02/05		
					(b) (6)	
28	Main	LLS	05/27/05	10/10/05		
					(b) (6)	
31	Large	TL	05/22/05	10/05/05		

Please send us the status including appointment date for the children listed above.

For patients who are truly lost, we recommend using the following web sites to search for their whereabouts (some of these were successfully used to locate patients in previous network trials):
www.555-1212.com
<file:///C:\Documents%20and%20Settings\higginsr\Local%20Settings\Temporary%20Internet%20Files\OLKC2\www.555-1212.com> (cost $20 for 100 lookups)

www.USA-people-search.com
<http://www.USA-people-search.com%20the%20cost%20$9-95> The cost for addresses, phone # birthdays searched is $9-95

www.anywho.com <http://www.anywho.com> . This is free but addresses may not be current

www.peopledata.com <http://www.peopledata.com> . this is $10 for address

www.find.intelius.com <http://www.find.intelius.com> use search by ss# for $49.95

Thank you for your ongoing commitment!

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

Hi Rose,

I attached the revised budget with a sensitivity analysis modeling total costs for the study under 4 scenarios in which local centers perform 0%, 25%, 75%, or 100% of the 6, 12 and 18 month telephone interviews (each interview allotted 2 hours of staff effort). Each scenario is described in detail on an individual worksheet in the attached Excel workbook. The scenarios and the total study costs are summarized below

Local Center Interviews (%)	Rochester Interviews (Centralized)	Total Study Cost
0	100	$144,866
25	75	$168,566
75	25	$215,966
100	0	$239,666

In addition to the cost issue, having each center conduct their own interviews raises the risk of non-uniform administration of the questionnaires. If each center conducts their own interviews, we'd try to standardize administration of the questionnaire by holding a one time training session for local study center telephone interviewers.

Although the NICHD cannot fund my K23 this cycle, I have not given up hope that the NHLBI will pick it up (I requested a dual assignment). If the K23 is funded, the Network's costs are diminished by approximately $60,000 over the duration of the study (see worksheets).

Please let me know if I can answer any questions.

Thanks

Tim Stevens

Center Costs **One Time Costs per Center**	**Hours**	**Cost/center ($43/hour)**	**Network Capitation/pt**	**# Centers**	**# Network Interviews**	**Rochester Costs $25/hr***	**Rochester Capitation/pt**	**# Rochester Interviews**	**Total Patients (# Survivors)**	**NICHD Network Centers** Portion of Total Cost 1st year**	**4 years**	**Rochester** Portion of Total Cost 1st year**	**4 years**	**Total Cost for the Entire Study**
RSRB - SUPPORT Consent Ammendment	5	$215		16						$3,440				$3,440
Interviewer Training (Includes training, airfare, room, board)	8	$1,200		16						$19,200				$19,200
Annual Costs Per Center														
RSRB renewal	2	$86		16							$1,376			$1,376
SubTotal (Direct Center Costs)										$22,640	$1,376			$24,016
Capitation Costs														
Cost per Infant (assuming 960 survivors undergoing interviews)														
Capitation														
Interview 1- Conducted by coordinators at NICHD Centers prior to discharge	0.5	$43	$22		700		$22	0	700		$15,050		$0	$15,050
Interview 2- at 6 months, local + Rochester	2	$43	$86	16	700	$25	$50	0	700		$40,200		$20,000	$60,200
Interview 3- at 12 months, local + Rochester	2	$43	$86	16	700	$25	$50	0	700		$40,200		$20,000	$60,200
Interview 4- at 18-22 months, local + Rochester	2	$43	$86	16	700	$25	$50	0	700		$40,200		$20,000	$60,200
Telephone Charges (Long distance charges)		$2,000				$0					$2,000		$0	$2,000
SubTotal Directs (Interviews)											$137,650		$60,000	$197,650
Outpatient Office Reimbursement for Chart Review						$25			700		$17,500		$0	$17,500
Postage											$0		$500	$500
SubTotal Directs (Chart Reviews)											$17,500		$500	$18,000
Sub Total Directs (Yearly Interval)										$22,640	$156,526		$60,500	$239,666
Grand Total Directs (Network and Rochester)											$179,166		$60,500	$239,666

Legend

* assumes $35,000/year with 29% benefits, working 2000 hours per year

** total costs shared between NICHD Neonatal Research Network (assuming Dr. Stevens' K23 Patient Oriented Research Award is funded, under review by NHLBI)

++total born by NICHD Neonatal Research Network (if Dr. Stevens' K23 Award is not funded)

Gray-Total Cost for the Entire Study (NICHD + Rochester)
Yellow- NICHD Portion of Total Costs
Blue- Rochester Portion of Total Costs
Turquoise- Incremental costs for local Network to conduct interviews

From:	Susan Hintz
To:	neil finer
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; dstevenson@stanford.edu; adas@rti.org; Jon.E.Tyson@uth.tmc.edu; jobea0@chmcc.org; bkh@rti.org; mbball@stanford.edu
Subject:	SUPPORT neuroimaging secondary forms and manual
Date:	Thursday, June 09, 2005 6:18:23 PM
Attachments:	NeuroSUPPORTManual[6-09-05].doc Central ReaderCranial US[MRI04]6-7-05.doc MedWatchForm[MRI02]6-3-05.doc MRI Enrollment Form[MRI01]6-9-05.doc MRI Scoring Form[MRI03]6-9-05.doc

Hello all,

Attached are final drafts of the SUPPORT neuroimaging secondary manual and forms. Please note that two of the forms (MRI03 and MRI04) are CENTRAL READER forms.

Unless I hear from someone to the contrary, I will forward these to Carolyn Petrie on Monday so they can be available for distribution at the Steering Committee meeting.

Thanks,

Susan

--

Susan R. Hintz, M.D.
Assistant Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

NEUROIMAGING AND NEURODEVELOPMENTAL OUTCOME: A SECONDARY TO SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL SUPPORT)

NICHD Neonatal Research Network

DRAFT
Manual of Operations

Revised: June 9, 2005

STUDY OBJECTIVE

This secondary is a prospective study of cranial US at 4-14 days ("early cranial US"), at 35-42 weeks postmenstrual age (PMA) ("late cranial US"), and brain MRI at 35-42 weeks PMA among infants enrolled in SUPPORT. We will evaluate and compare the capabilities of early and late cranial US and brain MRI to predict neuromotor and neurodevelopmental outcome at 18-22 months corrected age. We will also determine if ventilatory or oxygen saturation interventions are associated with differences in the outcomes of death or abnormal neuroimaging findings among patients enrolled in this secondary.

RESEARCH DESIGN AND METHODS

Study Design: This secondary to SUPPORT is a prospective study of traditional (cranial US at 4-14 days and 35-42 weeks PMA) and advanced (MRI at 35-42 weeks PMA) neuroimaging with respect to SUPPORT randomized ventilation and oxygen saturation interventions. The capabilities of these neuroimaging modalities to predict neurodevelopmental outcome at 18-22 months corrected age will be assessed.

Perinatal, demographic and neonatal data will be collected through the ongoing NICHD Neonatal Research Network Survey of Morbidity and Mortality Among VLBW Infants (401-1500g) and SUPPORT. Cranial US will be obtained at 4-14 days and at 35-42 weeks PMA, and brain MRI will be obtained within 7 days of late cranial US. For purposes of research outcomes, cranial US and brain MRI will be interpreted by central readers, but *clinical* interpretation will continue to be performed at individual Network sites. Neurodevelopmental examinations will be undertaken at 18-22 months corrected age as part of the NICHD Cooperative Multicenter Network of Neonatal Intensive Care Units: Follow-Up of ELBW Infants (401-1000g), and per SUPPORT protocol.

Study Population

Inclusion Criteria

- Enrolled in the NICHD Neonatal Research Network SUPPORT study
- Cranial ultrasound can be obtained on 4-14 days of age and at 35-42 weeks PMA
- Brain MRI can be obtained per study specifications (see below, Forms (Central MRI Reading form – MRI03)) at 35-42 weeks PMA.
    - If MRI cannot be performed by 42 weeks due to subject clinical condition, the late cranial US used for study purposes should also be delayed so that cranial US is within 7 days of the brain MRI.

Exclusion Criteria

- Presence of known or suspected congenital anomalies including:
    - Chromosomal anomalies
    - Complex congenital heart disease (PDA, small muscular VSD or PFO are NOT considered to be congenital heart disease for the purposes of this study)
    - Congenital infection (TORCH, untreated maternal HIV, syphilis)
- Lack of informed consent

Subject Enrollment

Screening: Each participating center will be responsible for devising a screening strategy to identify all potential participants using the study inclusion and exclusion criteria. Consent should be obtained at the time that SUPPORT consent is obtained, or soon thereafter. In some centers, particularly those in which MRI is the standard or routine near-term neuroimaging method, the consent for this secondary may be incorporated in the initial SUPPORT consent form. **However, the best approach and timing must be evaluated by each center; the process of attempting to obtain consent for the secondary should not prevent successful enrollment in the primary study.** Examples of both stand-alone and embedded consents have been distributed.

Informed consent: Each participating center will follow procedures for developing informed consents as set out by the local Institutional Review Board (IRB). It is expected that participating centers will approach the parents of all eligible infants to participate in this secondary study.

FORMS

SUPPORT Neuroimaging Secondary Enrollment Form – MRI01

Centers that participate in the neuroimaging secondary will be asked to complete form MRI01 for each infant enrolled in SUPPORT.

A. SUPPORT NEUROIMAGING SECONDARY ENROLLMENT

A. 1. Was this patient enrolled in the neuroimaging secondary?
Code "yes" if the patient was enrolled and go to section B.
Otherwise, code "no" and answer the following (A.1.a):

A.1.a. Indicate why the patient was not enrolled:
Code appropriate response (1-7).
1= Family refused
2= Physician refused
3= Unable to contact family
4= Patient died before consent could be obtained
5= Participation not offered because suspected/proven congenital infection (TORCH, untreated maternal HIV, syphilis)
6= Planned transfer to facility without MRI before 35 weeks
7= Other Reason (Specify)
If "other" (response 7), briefly describe reason(s) for non-enrollment.

B. EARLY CRANIAL US

Early cranial US should be obtained on days 4-14 of age.

- *If more than one cranial ultrasound is obtained during that period, the US with the most severe findings should be used.*
- *If all US obtained on days 4-14 of age have the same results, the US closest to 14 days should be used.*

- *If the first cranial US is obtained on day 15-21, the US may be entered as early cranial US – in this case, use the cranial US designated as the SUPPORT US for the main trial.*

Ultrasounds will be clinically evaluated at each center; each center is expected to counsel families with regard to US findings based on local interpretation. Ultrasounds will also be interpreted by central readers.

B.1. Date of early cranial US

Record the date on which the early cranial US was performed using the mm/dd/yyy format.

B.2. Was the study normal?

Code "yes" if the early cranial US was interpreted as normal by the local radiologist and go to question C.1. Otherwise, code "no" and code abnormality or abnormalities appropriately on questions B.2.(a-i).

B.2.a-i

Right and left hemisphere results should be coded based on the local radiology report. Note that MORE THAN ONE item may be recorded for each hemisphere. For sonographic reported that are limited to a grade of IVH (Papile grades I-IV), record as follows:

Grade I: code B.2.a Yes
Grade II: code B.2.b Yes
Grade III: code both B.2.b and B.2.c Yes
Grade IV: code B.2.d Yes

a. Blood/echodensity in germinal matrix/subependymal area?
   Code Y if blood or echodensity in germinal matrix/subependymal area is documented
b. Blood/echodensity in ventricle?
   Code Y if blood/echodensity in ventricle is documented
c. Ventricular size enlarged?
   Code Y if ventricle size enlargement or ventriculomegaly is documented, whether this finding is secondary to blood in ventricles or if no blood/echodensity is documented
d. Blood/echodensity in the parenchyma?
   Code Y if blood/echodensity documented in the parenchyma.
e. Cystic areas in the parenchyma
   Code Y if cystic area(s) are documented at the site of a previous parenchymal hemorrhage. Cystic periventricular leukomalacia should NOT be included in this category.
f. Cystic (echolucent) perventricular leukomalacia
   Code Y if echolucent/cystic periventricular leukomalacia or periventricular cysts were documented.
g. Echodense periventricular leukomalacia
   Code Y if echodense or echogenic periventricular leukomalacia was documented.
h. Porencephalic cyst

Code Y if porencephalic cyst was documented. Subependymal cysts or choroid plexus cysts should NOT be included in this category.

i. Infarct
Code Y if infarct was documented.

C. LATE CRANIAL US

Late cranial ultrasound should be obtained between 35-42 weeks PMA and within 7 days of brain MRI.

- *If MRI cannot be performed by 42 weeks, the late cranial US used for study purposes should also be delayed such that the late cranial US is within 7 days of the brain MRI.*

Ultrasounds will be clinically evaluated at each center; each center is expected to counsel families with regard to US findings based on local interpretation. Ultrasounds will also be interpreted by central readers.

C.1. Was late cranial US performed?
Code "yes" if a late cranial US was performed and continue to question C.1.b. Otherwise code "no" and answer question C.1.a.

C.1.a. If no, indicate why not:
Code appropriate response (1-5).
1= Patient Died
2= Family refusal
3= Physician refusal
4= Patient transferred or discharged
5= Other Reason (Specify)
If "other" (response 5), briefly describe reason(s) that late cranial US was not performed.

C.1.b. If yes, Date of late cranial US
Record the date on which the ultrasound was performed using the mm/dd/yyyy format.

C.1.c. If late cranial US was performed outside the 35-42 week window, indicate why.
Code a response (1-4) *only* if the late cranial US was performed outside the window.
1= US timing adjusted to be within 7 days of MRI due to patient instability
2= US timing adjusted to be within 7 days of MRI due to technical difficulties
3= Late neuroimaging obtained early due to patient discharge or transfer
4= Other reason (Specify)
If the response is "other" (response 4), briefly describe reason(s).

C.2. Was the study normal?
Code "yes" if the late cranial US was interpreted as normal by the local radiologist. Otherwise, code "no" and code abnormality or abnormalities appropriately on questions C.2.(a-e).

C.2.a-e

Right and left hemisphere results should be coded based on the local radiology report.

a. Ventricular size enlarged?

Code Y if enlarged ventricle size or ventriculomegaly was documented, whether this finding is secondary to blood in ventricle of if no blood/echodensity is documented.

b. Cystic (echolucent) periventricular leukomalacia?

Code Y if periventricular cysts or echolucent/cystic periventricular leukomalacia was documented.

c. Porencephalic cyst?

Code Y if porencephalic cyst was documented. Subependymal cysts or choroid plexus cysts should NOT be included in this category.

d. Infarct?

Code Y if infarct is documented

e. Shunt/resevoir in place?

Code Y if a shunt or resevoir is in place, otherwise code N.

D. BRAIN MRI

A brain MRI should be obtained (see specifications below under "FORMS" MRI03) from 35-42 weeks PMA and within 7 days of the late cranial ultrasound

- *If MRI is delayed due to subject instability, the late cranial US used for study purposes should also be delayed such that the late cranial US is within 7 days of the brain MRI.*

Brain MRI will be clinically evaluated at each center; each center is expected to counsel families with regard to MRI findings based on local interpretation. Central readers will interpret brain MRI for study purposes

D.1. Was a successful brain MRI performed?

Code "yes" if a successful brain MRI was performed and go to question D.1.b. Otherwise, code "no" and answer D.1.a.

If no,

D.1.a. Indicate why not:

Code appropriate response (1-5).

1= Attempted, but unsuccessful due to patient movement
2= Attempted, but unsuccessful due to patient instability
3= Not performed due to technical/MRI availability problems
4= Late family refusal
5= Other Reason (Specify)

If "other", briefly describe reason(s).

If yes,

D.1.b. Was more than one attempt necessary?

If more than one MRI attempt was required in order to obtain a successful study, code "yes" and go to question D.1.b.i. If only one attempt was required to obtain a successful MRI, code "no" and go to question D.1.c.

If Yes,

D.1.b.i. Indicate why:

If more than one MRI attempt was required, code appropriate response (1-3).
1= Patient movement
2= Technical/MRI problems
3= Other Reason (Specify)
If "other" (response 3), briefly describe reason(s).

D.1.c. If successful brain MRI performed, was pharmacologic sedation used?

If pharmacologic sedation was used, code "yes" and go to question D.1.c.i. If not, code "no" and go to question D.1.d.

D.1.c.i. If yes, indicate type of sedation used:

Code appropriate response (1-3).
1= Conscious sedation
2= Intubation/general anesthesia
3= Other (Specify)
If "other", briefly describe reason(s).

D.1.d. Date of brain MRI

Record the date on which the brain MRI was performed using the mm/dd/yyyy format.

E. US and MRI TRACKING

*Neuroimaging studies will be sent to RTI. The preferred form is CD rather than film. The early and late cranial US studies may be on one **CD for each patient** and the brain MRI should be on a **separate CD**. Thus, there should be at least two CD's for each patient if US and MRI have been performed. All CD's must also include embedded viewing software (DICOM viewer); an example of this type of software is ShowCase® by Trillium. There are many different viewer programs, but radiology departments are quite familiar with them.*

Each CD must be labeled with the following information:

Network Center #
Subject Network ID#
Type of neuroimaging study (i.e., early US, late US, brain MRI)
DATE of neuroimaging study

Neuroimaging studies should be sent to RTI at the address below. CD's may be batched and mailed to RTI once a month.

Betty Hastings
2245 South Miami Blvd.
Durham, NC 27703

E.1. Date US disk sent to RTI

Record the date on which thecranial US was sent to RTI using the mm/dd/yyyy format.

E.2. Date brain MRI disk sent to RTI

Record the date on which the brain MRI was sent to RTI using the mm/dd/yyyy format.

MedWatch Form – MRI02

Although extremely unlikely, any adverse events which occur at the time of or because of neuroimaging studies among enrolled patients will be documented on the MedWatch form, and submitted to NICHD and RTI within 24 hours of the event.

Stability of study patients for transport to a radiology suite for brain MRI will be assessed by the attending neonatologist at each participating site.

Central MRI reading form – MRI03

The MRI03 form (data form and key) will be used for central "gold standard" MRI reading.

MRI: Items 1-7 are mandatory for this protocol. If a Network center is also obtaining diffusion sequences (Item 8), tensor DTI with 6 directions may be performed, but 32 directions is preferred.

1. Sag. T1 CSE: TR 500 / TE 20 / Slice 3 / gap 1 / FOV 20 / matrix 256 x192 / NEX 1 (for localizer and corpus callosum).
2. Axial T1 CSE: 500 / 20 / 4 / 0 / 20 / 256 x 192 / 1
3. Axial T2 FSE: 3350/ 99 / 4 / 0 / 20 / 256x192 / 2 / ETL 8
4. Axial FLAIR: 9000 / 103 / 4 / 0 / 20 / 256x192 / 1-2 / TI 2200
5. Axial GRE: 500 / 15-30 / 4 / 0 / 20 / 256x192 / 1 / Flip angle 15
6. Axial or Coronal 3D SPGR: 24 / min. 8 / 1.5 / 0 / 20-22 (phase FOV 0.75) / 256x224 / 0.75 / FA 30
7. DWI: 4000 / min. 71/4/0/20/1128x128/1/b-value 1000/# directions - 6
8. Tensor DTI: 4000 / min. 71 / 4 / 0 / 20 / 128x128 / 1 / B-value 1000 / # directions - 32

General Information
The following information should be provided at the time of completion of this form:
A. Identification:
This section provides important information regarding the MRI currently being read:
1. Reader: Enter the initial of the individual who read this MRI.
2. Date Read: Enter the month/day/year of the MRI was read
3. Date of MRI: Enter the month/day/year of the MRI
4. PCA in Weeks and Days at MRI: This will be provided by RTI
5. Quality: Indicate whether the quality of the MRI was good or poor
6. Readable: Answer Yes or No to indicate if the MRI was readable.
7. All Necessary Sequences; Answer Yes or No to indicate if all the necessary sequences were present. If No, indicate what is missing.
8. Normal Reading: Answer Yes or No to indicate if the reading was normal. If the answer to this question is No, the remainder of the form should be completed.

B. SIGNAL ABNORMALITIES
REGION AND SITE

REGION	CODE	SITE		CODE
CEREBRAL	C	Frontal		
			cortical	FC
			subcortical	FSC
			periventricular	FPV
		Temporal		
			cortical	TC

			subcortical	TSC
			periventricular	TPV
		Parietal		
			cortical	PC
			subcortical	PSC
			periventricular	PPV
		Occipital	cortical	OC
			subcortical	OSC
			periventricular	OPV
CEREBELLAR	BEL	Vermian		V
		Hemespheric		H
BASAL GANGLIA	BG	Putamen		P
		Caudate		CAU
		Globus Pallidus		GP
THALAMUS	T			
INTERNAL CAPSULE	IC			
BRAINSTEM	BS	Medulla		M
		Pons		P
		Midbrain		MID
CORPUS CALLOSUM	CC	Genu		G
		Body		B
		Splenium		SPL
PITUITARY	PIT			
HYPOTHALAMUS	HY			
OPTIC CHIASM	OP			
EXTRA-AXIAL	EX	Subarachnoid		SAR
		Subdural		SDR
		Epidural		EPI
VASCULAR	VAS	Arterial		ART
		Venous		VEN
OTHER	OTH			

**Note location and specifics at END OF MRI SCORING FORM

SIDE	**CODE**
Right	R
Left	L

T1, T2, FL, GRE

INTENSITY	**CODE**
hypointense	HYPO
isointense	ISO
hyperintense	HYPER

FOCAL/DIFFUSE	**CODE**
if focal	F
if diffuse	D

GM/WM	**CODE**
if gray matter	GM
if white matter	WM

SIZE: Enter MEASURED diameter of lesion, i.e., 3 = 3mm, 4= 4mm, etc.

TYPE: **GUIDELINES for interpretation**

Cystic abnormalities: T1 hypo T2 hyper, FL hypo

Non-Cystic abnormalities: T1 hyper or hypo T2 hyper FL hyper

Hemorrhage or mineralization: GRE hypo +/- T1 hyper T2 hypo

Type	CODE
Cystic	CYS
Non-Cystic	NCYS
Hemmorhage/Mineral	HMN

C. MATURATION AND DEVELOPMENT

GRAY MATTER MATURATION [1, 2, 3]

For each hemisphere, mark level of maturation

Stage	Cortical maturation markers
G0	Frontal and occipital cortex completely smooth, insula widely open
G1	Frontal cortex still smooth, but some sluci in occipital cortex
G2	Frontal and occipital cortex with some convolutions, frontal sulci shallow
G3	Frontal and occipital cortex folded and rich in sulci, insula more convoluted and infolded
G4	Secondary gyri present transverse and inferior temporal; anterior and posterior orbit gyri
G5	Teritiary inferior temporal and infereior occipital gyri and sulci present. White matter now isointense with gray matter on T1

SUBARACHNOID SPACE [4]

Normal = <4 mm

Mild-moderate enlargement = 4-6 mm

Marked enlargement = >6 mm

WHITE MATTER MATURATION [1, 5]

For each hemisphere, mark level of maturation noted on both T1 and T2

Stage	Myelination
W0	Immature (<30 week) myelination patter - i.e. brain stem not myelinated, etc.
W1	brain stem, dorsal aspect of pons
W2	ventral pons, cerebellar medulla
W3	PLIC, lenticular nucleus, thalamus
W4	corona radiata
W5	corticospinal tracts of the precentral and postcentral gyri

CORPUS CALLOSUM

Provide SAGITTAL measured width at each of the following

Genu

Body

Splenium

LATERAL VENTRICLE SIZE, ASYMMETRY AND DISPROPORTION [6, 7]

SIZE: Measure ventricular/brain index (V/B index) on CORONAL IMAGES. Mark Y (yes) or N (no)

Frontal horn ABNORMAL = V/B ratio>0.35

Midbody ABNORMAL = V/B ratio>0.35

Trigone ABNORMAL = V/B ratio >0.60

ASYMMETRY:

Mark "yes" in appropriate box if one ventricle is clearly larger than the other

DISPROPORTION:

Record "yes" if clear disproportionate shape of lateral ventricle, including but not limited to "squared"

D. INTRAVENTRICULAR CONTENT

Describe presence or absence of choroid cyst and hemorrhage as indicated.
Describe presence or absence of intraventricular hemorrhage, shunt, and mineralization as indicated

E. OTHER
Record maximum transverse and vertical dimension of fourth ventricle and maximum transverse dimension of third ventricle in millimeters.

BIBLIOGRAPHY

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4. Valkama AM, et. al. Acta Paediatr 2000;89:348-355
5. Counsell S, et. al. AJNR 2002;23:872-881
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Central cranial US reading form – MRI04

The MRI04 form will be used for central "gold standard" cranial US reading. It is similar to the central reader form used for the PiNO cranial US central reading.

APPENDIX A - FORMS

See Attached forms (MRI01, MRI02, MRI03, MRI04)

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants MRI04 Rel 1 June 7, 2005

Support Neuroimaging Secondary

Draft Central Cranial US Reading Form

Center: Network No: Birth No

A. IDENTIFICATION

1. READER: ___ ___ ___ INITIALS
2. DATE READ: __ __/__ __/__ __ __ __ MONTH DAY YEAR
3. READING: ____
4. DATE OF SONOGRAM: __ __/__ __/__ __ __ __

5. QUALITY: GOOD POOR
6. READABLE: YES NO
8. ALL NECESSARY VIEWS AVAILABLE: YES NO
9. NORMAL READING: YES NO

ULTRASOUND RESULTS	Left		Right	
	Yes	No	Yes	No
B. ECHODENSITY SITE				
1. Echodensity present				
If Yes, mark all that apply				
a. Subependymal				
b. Periventricular (PVL)				
If Yes, mark all that apply				
1. Frontal				
2. Temporal				
3. Parietal				
4. Occipital				
c. Intraventricular				
1) If Yes,				
< 25 % filled				
25-50 % filled				
> 50% filled				
d. Intracerebral				
If Yes, mark all that apply				
1. Frontal				
2. Temporal				
3. Parietal				
4. Occipital				
5. Thalamus				
6. Posterior Fossa				
e. Other				

	Left		Right	
	Yes	No	Yes	No
C. ECHOLUCENCY SITE				
1. Echolucency present				
If Yes, mark all that apply				
a. Subependymal				
b. Periventricular (PVL)				
If Yes, mark all that apply				
1. Frontal				
2. Temporal				
3. Parietal				
4. Occipital				
c. Intracerebral				
If Yes, mark all that apply				
1. Frontal				
2. Temporal				
3. Parietal				
4. Occipital				
d. Parenchymal Cyst				
e. Other				
D. OTHER PARENCHYMAL				
1. Other Parenchymal				
If Yes, mark all that apply				
a. Calcification				
b. Cerebral edema				
c. Cortical atrophy				
d. Extra axial fluid				
e. Infarct				
f. LS Branching				
g. Other				

	Left		Right	
	Yes	No	Yes	No
E. VENTRICLES				
1. Ventricle abnormality				
a. If Yes,				
Mild increase				
Moderate increase				
Severe increase				
Slit Ventricles				
2. Choroid abnormality				
If Yes, mark all that apply				
a. Cyst				
b. Hemorrhage				
c. other				
F. HEMORRHAGE CLASSIFICATION				
1. Hemorrhage				
If Yes,				
a. Papile Classification				
Grade I				
Grade II				
Grade III				
Grade IV				
Indeterminate				
G. STRUCTURAL ABNORMALITIES				
1. Structural abnormality				

If Yes, comments:

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Draft Support Neuroimaging Secondary

MEDWATCH FORM

MRI02 Rel 1.0
June 3, 2005

Center: ___ Site No: ___ Network No. _____ Birth No: ___ Mother's Initials: _____ Page 1 of 1

SEND TO RTI AND NICHD WITHIN 24 HOURS

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ___ of ___

Form Approved: OMB No. 0910-0291 Expires: 11/30/99
See OMB statement on reverse

FDA Use Only
Triage unit sequence #

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient Identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ___ lbs or ___ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ___ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: ___
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1
   #2
2. Dose, frequency & route used
   #1
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1
   #2
4. Diagnosis for use (indication)
   #1
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only)
   – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: ___
5. Expiration date (mo/day/yr)
6. model # ___
   catalog # ___
   serial # ___
   lot # ___
   other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on ___ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address
   phone #
2. Health professional? ☐ yes ☐ no
3. Occupation
4. Also reported to
   - ☐ manufacturer
   - ☐ user facility
   - ☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to: 1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Center: __ __ Site: ___ Network No. __ __ __ __ Birth No. __ Mother's Initials: __ __ __

A. SUPPORT NEUROIMAGING SECONDARY ENROLLMENT

1. Was this patient enrolled in the neuroimaging secondary? Y N

   If Yes, go to Section B.

   a. If No, indicate why the patient was not enrolled: ___

      1. Family refused
      2. Physician refused
      3. Unable to contact family
      4. Patient died before consent could be obtained
      5. Participation not offered because suspected/proven congenital infection (TORCH, untreated maternal HIV, syphilis)
      6. Planned transfer to facility without MRI before 35 weeks
      7. Other Reason (Specify)_____

B. EARLY CRANIAL US

1. Date of early cranial US (*US with the most severe findings performed on day 4-14 or the US* designated as *the "SUPPORT" US for the main trial if the first cranial US performed on day 15-21)* : __ __/__ __/__ __ __ Month Day Year
2. Was the study normal? Y N

   If **No**,

	(1) RIGHT		(2) LEFT	
a. Blood/echodensity in germinal matrix/subependymal area?	Y	N	Y	N
b. Blood/echodensity in ventricle?	Y	N	Y	N
c. Ventricular size enlarged?	Y	N	Y	N
d. Blood/echodensity in the parenchyma?	Y	N	Y	N
e. Cystic area(s) in the parenchyma?	Y	N	Y	N
f. Cystic (echolucent) periventricular leukomalacia?	Y	N	Y	N
g. Echodense periventricular leukomalacia?	Y	N	Y	N
h. Porencephalic cyst?	Y	N	Y	N
i. Infarct?	Y	N	Y	N

C. LATE CRANIAL US *(Note: Cranial US should be performed within 7 days of brain MRI)*

1. Was the late cranial US performed? Y N

   a. If No, Indicate why not: ___

      1. Patient Died
      2. Family refused
      3. Physician refused
      4. Patient transferred or discharged
      5. Other Reason (Specify)_____

   b. If Yes, date of late cranial US: __ __/__ __/__ __ __ Month Day Year

   c. If late cranial US was performed outside the 35 - 42 week window, indicate why: ___

      1. US timing adjusted to be within 7 days of MRI due to patient instability
      2. US timing adjusted to be within 7 days of MRI due to technical difficulties
      3. Late neuroimaging obtained early due to patient discharge or transfer
      4. Other reason (Specify_____)

2. Was the study normal? Y N

   If **No**,

	(1) RIGHT		(2) LEFT	
a. Ventricular size enlarged?	Y	N	Y	N
b. Cystic periventricular leukomalacia?	Y	N	Y	N
c. Porencephalic cyst?	Y	N	Y	N
d. Infarct?	Y	N	Y	N
e. Shunt/resevoir in place?	Y	N	Y	N

D. **BRAIN MRI** ***(Note: Brain MRI should be performed within 7 days of late cranial US***

1. Was a successful brain MRI performed? Y N

a. If No, Indicate why not: ___

1. Attempted, but unsuccessful due to patient movement
2. Attempted, but unsuccessful due to patient instability
3. Not performed due to technical/MRI availability problems
4. Family withdrew consent
5. Other Reason (Specify)_____

b. If Yes, was more than one attempt necessary? Y N

If Yes,

i) Indicate why: ___

1. Patient movement
2. Technical/MRI problems
3. Other Reason (Specify):_____

c. If successful brain MRI performed, was pharmacologic sedation used? Y N

i) If Yes, indicate type of sedation used: ___

1. Conscious sedation
2. Intubation/general anesthesia
3. Other (Specify):_____

d. Date of brain successful MRI: __ __/__ __/__ __ __
Month Day Year

E. US and MRI TRACKING (See Manual for instructions):

1. Date US disk sent to RTI: __ __/__ __/__ __ __
Month Day Year
2. Date brain MRI disk sent to RTI: __ __/__ __/__ __ __
Month Day Year

NICU Network

NEUROIMAGING AND NEURODEVELOPMENTAL OUTCOME: A SECONDARY TO SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL (SUPPORT)
DRAFT CENTRAL MRI READING FORM

MRI03
June 9, 2005

Center: __ __ Site __ Network No: __ __ __ __

GENERAL INFORMATION

A. IDENTIFICATION

1. READER: __ __ __ Initials
2. DATE READ: __ __/__ __/__ __ __ __ MONTH DAY YEAR
3. DATE OF MRI: __ __/__ __/__ __ __ __ MONTH DAY YEAR
4. PCA IN WEEKS AND DAYS AT MRI: __ __ . __
5. QUALITY: GOOD POOR
6. READABLE: YES NO
7. ALL NECESSARY SEQUENCES, If No, what is missing? _____ YES NO
8. NORMAL READING: If No, completed the remainder of the form YES NO

MRI READING

B. SIGNAL ABNORMALITIES:

1. Are signal abnormalities present? Yes No
   If No, continue to "Maturation and Development" Section.
   If Yes, describe each lesion below:

Lesion Number:	Region	Site	Side	T1	T2	FL	GRE	Focal/Dif GM/ WM	Size	TYPE
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										

If more than 10 lesions, complete additional signal abnormality sheet.

C. MATURATION AND DEVELOPMENT:

1. GRAY MATTER

a. Cortical maturation markers (check only one appropriate box per each hemisphere)

	Left	Right
1. G 0		
2. G 1		
3. G 2		
4. G 3		
5. G 4		
6. G 5		

b. Subarachnoid space enlargement (check only one appropriate per for each hemisphere)

	Left	Right
1. Normal		
2. mild-mod		
3. Marked		

2. WHITE MATTER

a. Markers of myelination (Check only one appropriate box per hemisphere for T1 and T2))

	Left		Right	
	T1	T2	T1	T2
1. W 0				
2. W 1				
3. W 2				
4. W 3				
5. W 4				
6. W 5				

b. Corpus Callosum Measured Width (Sagittal view)

1. genu	__ __ __ mm
2. body	__ __ __ mm
3. splenium	__ __ __ mm

c. Lateral Ventricle Size

V/B INDEX Abnormal?	Left		Right	
	Yes	No	Yes	No
1. Frontal horn				
2. Midbody				
3. Trigone				

d. Lateral Ventricle asymmetry and disproportion Yes No

If Yes, complete below:

	Yes	No
1. Left greater than right		
2. Right greater than left		
3. Right disproportion		
4. Left disproportion		

D. INTRAVENTRICULAR CONTENT

	Left		Right	
	Yes	No	Yes	No
1. Choroid cyst				
2. Choroid hemorrhage				
3. LATERAL VENTRICLES				
A. Hemorrhage?				
1. Grade I				
2. Grade II				
3. Grade III				
4. Grade IV				
B. Shunt present?				
C. Mineralization present?				

E. OTHER

		Measured size
1. THIRD VENTRICLE	Transverse	
2. FOURTH VENTRICLE	Transverse	
	Vertical	

	Left		Right	
3. STRUCTURAL ABNORMALITIES	Yes	No	Yes	No

COMMENTS:

From: Higgins, Rosemary (NIH/NICHD)
To: Raju, Tonse (NIH/NICHD)
Subject: Re: Pulmonary Outcomes for Support
Date: Thursday, June 09, 2005 3:23:38 PM

I will keep my fingers crossed!!

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Raju, Tonse (NIH/NICHD) <rajut@mail.nih.gov>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Thu Jun 09 15:22:29 2005
Subject: RE: Pulmonary Outcomes for Support

While HL's funding cut off is 170; but they have 3-4 around 170, and therefore they are not sure if they can pick up this one. We shall know in about 2 weeks after their council.

Tonse N. K. Raju, MD
Medical Officer/Program Scientist
Pregnancy and Perinatology Branch
CDBPM/NICHD; National Institutes of Health
6100 Executive Blvd, Room 4B03
Bethesda, MD, 20952.
(For Fed Ex: Rockville, MD, 20852)
Phone: 301-402-1872
Fax 301-496-3790
NIH Homepage:http://www.nih.gov
PPB HOMEPAGE
http://www.nichd.nih.gov/about/cdbpm/pp/pp.htm

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD)
Sent: Thursday, June 09, 2005 10:11 AM
To: Raju, Tonse (NIH/NICHD)
Subject: Fw: Pulmonary Outcomes for Support

FYI

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-----Original Message-----
From: Stevens, Timothy <Timothy_Stevens@URMC.Rochester.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; 'nfiner@ucsd.edu' <nfiner@ucsd.edu>; Phelps, Dale <Dale_Phelps@URMC.Rochester.edu>
Sent: Wed Jun 08 21:54:04 2005
Subject: RE: Pulmonary Outcomes for Support

Hi Rose,

I'm meeting with Dale tomorrow to review and update the budget for the Pulmonary Outcomes follow on study. The budget to the NICHD will depend on whether my K23 is funded. Dr. Raju said that I am likely just above the payline at NICHD. Fortunately, I asked for a dual assignment with NHLBI. I understand that my K23 is under consideration through that institute. It would be nice to pull in NHLBI funding to help support the Pulmonary Outcomes Study. Do you know when the NHLBI funding decision will be available?

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Cc: Phelps, Dale
Subject: FW: Pulmonary Outcomes for Support

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Cc: JANET MORGAN; BVohr@WIHRI.org
Subject: Fwd: Pulmonary Outcomes for Support

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One other interesting article that addresses the llimited accuracy of reported wheezing was published last year in Arch Dis Child 89:540-543 by Lowe et. al.

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Subject: Re: Fwd:

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Hi,

We appreciate the hard work and dedication of all the sites in their participation in the Preemie iNO trial. As you know, a crucial component of this trial is neurodevelopmental outcome at 18-22 months corrected age. To assure the best possible follow-up, we ask you to look into the following follow-up issues, and respond to concerns as soon as possible. Please note that, even if the follow-up window has "closed", the neurodevelopmental follow-up visit should still be done.

Preemie iNO Surviving Infants Not Followed Up

Mother First	Mother Last	Follow-up Study Start	Follow-up Study End	Gestational Age Birth Date	Gestational Age Weeks
Center		ID			

Study
Name Name Date Date

4:Univ. of Texas Dallas (b) (6) [redacted] 32
Main
PR THO 07/10/04 11/23/04

(b) (6) [redacted] 31
Main
SMP 12/31/04 05/16/05

(b) (6) [redacted] 28
Main
AC 05/04/05 09/17/05

(b) (6) [redacted] 27
Main
LMV 05/19/05 10/02/05

(b) (6) [redacted] 32
Main
MR 04/19/05 09/02/05

(b) (6) [redacted] 28
Main
LLS 05/27/05 10/10/05

(b) (6) [redacted] 31
Large
TL 05/22/05 10/05/05

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For patients who are truly lost, we recommend using the following web sites
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<file:///C:\Documents%20and%20Settings\higginsr\Local%20Settings\Temporary%20Internet%20Files\OLKC2\www.555-1212.com> (cost $20 for 100 lookups)

www.USA-people-search.com
<http://www.USA-people-search.com%20the%20cost%20$9-95> The cost for addresses, phone # birthdays searched is $9-95

www.anywho.com <http://www.anywho.com> . This is free but addresses may not
be current

www.peopledata.com <http://www.peopledata.com> . this is $10 for address

www.find.intelius.com <http://www.find.intelius.com> use search by ss# for
$49.95

Thank you for your ongoing commitment!

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

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(For overnight delivery, use Rockville, MD 20852)

301-435-7909

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higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

From: Raju, Tonse (NIH/NICHD)
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: Pulmonary Outcomes for Support
Date: Thursday, June 09, 2005 3:22:42 PM

I also spoke to Tim today.

Tonse N. K. Raju, MD
Medical Officer/Program Scientist
Pregnancy and Perinatology Branch
CDBPM/NICHD; National Institutes of Health
6100 Executive Blvd, Room 4B03
Bethesda, MD, 20952.
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Mother First Name	Mother Last Name	Follow-up Study Start Date	Follow-up Study End Date	Gestational Birth Age Weeks	
Center Name		ID			
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PR	THO	07/10/04	11/23/04		
		(b) (6)		31	
Main					
SMP		12/31/04	05/16/05		

(b) (6) [redacted] 28
Main
AC 05/04/05 09/17/05

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www.USA-people-search.com
<http://www.USA-people-search.com%20the%20cost%20$9-95> The cost for addresses, phone # birthdays searched is $9-95

www.anywho.com <http://www.anywho.com> . This is free but addresses may not
be current

www.peopledata.com <http://www.peopledata.com> . this is $10 for address

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From:	Archer, Stephanie (NIH/NICHD) [E]
To:	Abbot Laptook (alaptook@WIHRI.org); Abhik Das (adas@rti.org); Bradley.yoder@hsc.utah.edu; Kurt Schibler (kurt.schibler@cchmc.org); Marie Gantz (mgantz@rti.org); Michele C. Walsh (mcw3@cwru.edu); Nancy Newman (nxs5@cwru.edu); Neil Finer (nfiner@ucsd.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Wade Rich (wrich@ucsd.edu); "Wally Carlo (wacarlo@uab.edu)"
Cc:	Kristin Zaterka-Baxter (kzaterka@rti.org)
Subject:	PAS Abstracts | Early Bird Proposals, SUPPORT
Date:	Monday, June 07, 2010 9:24:32 AM
Attachments:	LeVan, Changes in Therapy and Outcomes Associated with SUPPORT Trial, 2010-05-24 SUPPORT & GDB.doc Carlo, SUPPORT RoP, 2010-05-17 SUPPORT.doc

Wally,

Here are the other PAS Abstract proposals.

Stephanie

Attached are the early bird proposals for PAS abstracts for SUPPORT:

- LeVan, Changes in Therapy and Outcomes Associated with the SUPPORT Trial [GDB and SUPPORT]
- Carlo, Retinopathy of prematurity and actual oxygen saturations: A secondary protocol of the SUPPORT Trial [SUPPORT data only]

Robin Webb is setting up a call to discuss these proposals.

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

Application to the Full Steering Committee

Changes in Therapy and Outcomes Associated with The SUPPORT Trial

Jaclyn LeVan, DO, Myra Wyckoff, MD, Pablo Sánchez, MD, Roy Heyne, MD, Chul Ahn, PhD, Mambarath Jaleel, MD, Luc P Brion, MD (PI), **Finer NN**, **Carlo WA**, Walsh MC, Rich W, Gantz M, Laptook AR, Yoder BA, Faix RG, **Das A**, Poole WK, Ambalavanan N, Schibler K, Donovan E, Newman N, Frantz III ID, Sánchez PJ, Buchter S, Morris BH, Laroia N, Poindexter BB, Cotton M, Van Meurs KP, Sood B, Duara S, O'Shea TM, Bell EF, Bhandari V, Watterberg KL, **Gantz M**, **Stoll B**, **Higgins RD**

For the NICHD Neonatal Research Network

Version 32

5/2317/2010

A. ABSTRACT:

We propose an observational study (before/after study design) of GDB data and a survey of institutions in the NRN to examine the changes in clinical practices and outcomes following the results of the SUPPORT Trial.

B. STATEMENT of the PROBLEM

The SUPPORT trial (Finer; Carlo, in press) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24 0/7ths weeks to 27 6/7ths weeks were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within 1 hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%. The results of the SUPPORT trial were finalized in November 2009 and officially released in May 2010. . The rates of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups. In the CPAP group infants had lower rates of intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day 7.

The rates of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) were not significantly different between the two oxygen saturation target groups. However, in the lower oxygen saturation target group, death was significantly more frequent while severe retinopathy of prematurity among survivors occurred significantly less often.

In a retrospective study conducted at Parkland Memorial Hospital we found that the frequency of delivery room intubation among gestational age-matched infants (who did not participate in the SUPPORT trial) decreased significantly after initiation of the SUPPORT trial (Brion 2008).

C. HYPOTHESES:

1. We hypothesize that release of the results of the SUPPORT Trial will be followed by (1) a decrease in frequency of endotracheal intubation in the delivery room in preterm infants with gestational age between 24 0/7 and 27 6/7 weeks, and that the decrease in the frequency of delivery room intubation in each neonatal research network (NRN) center would depend on baseline rate before the trial and (2) institution-specific changes in target oxygen saturation.
2. We hypothesize that the release of the SUPPORT trial results will not affect the rates of death or bronchopulmonary dysplasia at 36 weeks postmenstrual age (BPD, defined by the physiologic definition), death at any time while hospitalized or severe retinopathy of prematurity (ROP), BPD (defined by the physiologic definition), BPD (defined by oxygen requirement at 36 weeks) and ROP among preterm infants, but will reduce the frequency of mechanical ventilation or death at day 7 and the frequency of use of corticosteroids for BPD.
3. We hypothesize that changes in ROP (increase) and mortality rate (decrease) will occur in centers that used low oxygen saturation target (85 to 89% or lower) before the SUPPORT trial and have now increased this target (as reported by the centers to a survey

conducted as part of this concept proposal) to a value similar to the higher range used in the SUPPORT trial, i.e., 91 to 95%.

D. SPECIFIC AIMS:

1. To determine the impact of the results of the SUPPORT trial on clinical practice, specifically, (1) the incidence of endotracheal intubation in the delivery room in preterm inborn infants and (2) target oxygen saturation in the NRN centers
2. To determine the impact of the results of the SUPPORT trial on outcomes in preterm inborn infants with gestational age between 24 0/7 and 27 6/7 weeks, including: incidence of death or BPD at 36 weeks postmenstrual age (defined by the physiologic definition, death at any time while hospitalized or severe ROP, BPD [defined by the physiologic definition], BPD [defined by oxygen requirement at 36 weeks postmenstrual age], ROP, mechanical ventilation or death at day 7, use of postnatal corticosteroids for BPD, mortality rate in the whole group and mortality rate in each stratum (24 0/7ths weeks to 25 6/7ths weeks and 26 0/7ths weeks to 27 6/7ths weeks).

E. RATIONALE/JUSTIFICATION:

The SUPPORT trial showed no difference in primary outcome between the two respiratory support strategies but advantages of early CPAP on three secondary outcomes. Therefore, we expect that providers using endotracheal intubation as standard of care in the delivery room before the SUPPORT trial would change their attitudes towards more CPAP and less intubation after the release of the SUPPORT Trial results. The intubation rate among extremely low birth weight infants was high (80%) in NRN centers in 1993-1997 (Shankaran 2002) and was still high at Parkland Memorial Hospital in 2005 (Brion 2008). Since there is substantial heterogeneity in therapy and outcome across NRN centers, we expect that the change in practice after release of the results of the SUPPORT trial would be inversely related with the baseline rate of intubation in each center.

The SUPPORT trial showed no difference in primary outcome between the two oxygen saturation targets, but showed significantly higher mortality and lower rate of ROP with low oxygen saturation target. Specifically the trial showed that targeting lower oxygen saturation resulted in one additional death for approximately every 2 cases of severe ROP prevented. Since the SUPPORT trial is the first trial to show that targeting low oxygen saturation significantly increases mortality in extremely preterm infants, we might expect that some centers or providers using low oxygen saturation target before the SUPPORT trial would consider increasing their target levels after release of the results of the SUPPORT trial.

F. BACKGROUND/PREVIOUS STUDIES:

<u>CPAP vs. intubation and surfactant:</u>

Prophylactic and early natural surfactant administration at less than 2 hours of life significantly decreases mortality, air leak, and death or BPD in intubated preterm infants who are either at risk for respiratory distress syndrome (< 30 weeks of gestational age) or with respiratory distress syndrome (Soll 1997, Soll 1999). Several studies have suggested a benefit for early CPAP for preterm infants with respiratory distress syndrome, including a decrease in the need for mechanical ventilation among very preterm infants without an

increase in morbidity (Avery 1987, Van Marter 2000, VanPee 2007, Jonsson 1997, Gitterman 1997) except for pneumothorax (summary relative risk 2.36; 95% confidence interval 1.25, 5.54) (Ho 2002). In one observational study, 76% of infants with a birth weight ≤ 1250 g who were initially treated with CPAP did not require intubation within 72 hours (Ammari 2005).
The NICHD Feasibility Trial (Finer 2004) was designed to determine the feasibility of randomizing ELBW infants of < 28 weeks' gestation to CPAP/positive end expiratory pressure (PEEP) or no CPAP/PEEP during resuscitation immediately after delivery, avoiding routine delivery room intubation for surfactant administration. Forty-five percent (47 of 104) of infants < 28 weeks' gestation required intubation for resuscitation in the delivery room. CPAP/ PEEP in the delivery room did not affect the need for intubation at birth or during the subsequent week. Overall, 20% of infants did not need intubation by 7 days of life.

Three multicenter RCTs have compared early CPAP with intubation in the delivery room. The IFDAS trial (Thomson 2001) showed no significant difference between 4 groups (Elective intubation with surfactant administration and extubation within 2 hrs; early nasal CPAP with selective short intubation for surfactant administration; elective intubation with surfactant administration and artificial ventilation; selective intubation with surfactant administration and artificial ventilation based on clinical criteria) in total respiratory support until estimated date of delivery or discharge home (if earlier) and other neonatal complications. However, this study was not powered for any of the outcomes.

The COIN trial (Morley 2008) randomized 610 infants from 25 0/7 to 28 6/7 weeks gestation, who were able to breathe at 5 minutes of age and had evidence of respiratory distress. Infants were randomized, either to intubation and ventilation, or to CPAP at 8 cm H_20 with intubation for those who met failure criteria. The primary outcome of death or BPD at 36 weeks was similar in the CPAP and in the intubation arms 33.9% vs. 38.9%, (odds ratio=0.58 to 1.12; P=0.19). Infants randomized to CPAP had a higher frequency of pneumothorax (9.1% vs. 3.0%, p=.001) and a lower frequency of death or need for oxygen at 28 days (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006).

<u>Oxygen administration upon admission to the neonatal intensive care unit:</u>
Trials published in the 1950's comparing restricted (≤ 50%, only for clinical indication or cyanosis) versus unrestricted (routine for 2-4 weeks or until reaching 1500 g) ambient oxygen in very low birth weight infants upon admission or within the first 48 hours showed a significant reduction in ROP and severe ROP (Duc 1992, Askie 2009) without a significant change in mortality (risk difference 4.9%, 95% CI -5.2, + 14.9; risk ratio 1.23, 95% CI 0.80, 1.90). Observational studies have suggested that targeting low oxygen saturation upon admission in very preterm infants may reduce the risk of ROP (Tin 2007) without increasing mortality (Chow 2003, Deulofeut 2007, Wright 2006). No randomized trials until the SUPPORT trial have assessed the effect of targeting different oxygen saturation levels upon admission on morbidity and mortality in very preterm infants.

SUPPORT Trial (extracted from Finer, in press and Carlo, in press):

The SUPPORT trial (Finer, in press; Carlo, in press) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24 0/7ths weeks to 27 6/7ths weeks were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within 1 hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%. The primary outcome of the CPAP vs. surfactant trial was the rate of composite primary outcome of death or bronchopulmonary dysplasia (BPD) defined by requirement for oxygen or positive pressure support with CPAP or mechanical ventilation at 36 weeks (with an attempt to remove oxygen in neonates receiving less or equal to 30% oxygen). The primary outcome of the oxygen saturation trial was a composite of severe retinopathy of prematurity (threshold retinopathy, or surgical ophthalmologic intervention, or the use of bevacizumab) and/or death before discharge from the hospital.

The results of the SUPPORT trial were finalized in November 2009 and officially released in May 2010.. The study enrolled 1316 infants. The rates of the primary outcome were not significantly different between the CPAP and surfactant groups (47.8% vs. 51.0%, Relative risk (RR) 0.95 (95% Confidence interval (CI) 0.85, 1.05, adjusting for gestational age, center and familial clustering). In the CPAP group infants had lower rates of intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day 7. The rates of other adverse neonatal outcomes were not significantly different in the 2 groups.

The rates of the primary outcome (severe retinopathy of prematurity [ROP] or death) were not significantly different between the two oxygen saturation target groups (28.3 vs. 32.1%, respectively; relative risk (RR) 0.90; 95% confidence interval (CI) 0.76, 1.06; p= 0.21). Death occurred more frequently in the lower oxygen saturation target group (19.9 vs. 16.2%; RR 1.27; CI 1.01, 1.60; p= 0.04) while severe retinopathy among survivors occurred less often in these infants (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p<0.001). However, in the lower oxygen saturation target group, death was significantly more frequent, while severe retinopathy of prematurity among survivors occurred significantly less often. The rates of other adverse neonatal outcomes were not significantly different in the 2 groups.

Retrospective study at Parkland Memorial Hospital:

A retrospective study (Brion 2008) was conducted at Parkland Memorial Hospital to assess the impact of SUPPORT trial initiation in July 2005 on patient management and short-term outcomes in non-participant preterm infants. We analyzed two prospective databases: the resuscitation registry and the neonatal intensive care unit (NICU) database. We included all inborn infants with gestational age < 35 weeks during 3 epochs: 01/03-07/05 (1st Epoch), 07/05-12/05 (2nd Epoch) and 01/06-11/07 (3rd Epoch), corresponding, respectively, to 30 months that preceded enrollment into SUPPORT, the first 6 months of SUPPORT enrollment, and the next 23 months of SUPPORT enrollment. We excluded infants who received comfort care only and those enrolled in the SUPPORT trial. Among neonates < 28 weeks of gestational age, initiation of the SUPPORT trial was associated with significant decreases in the rates of intubation in the delivery room or the

NICU, and surfactant administration, and an increase in the rate of delivery room CPAP.

Infants < 28 wk gestational age (n=267)				
	1st Epoch N=160	2nd Epoch N=17	3rd Epoch N=90	P
Delivery room intubation	87%	77%	52%	<0.001
Delivery room CPAP	30%	47%	50%	0.004
Early NICU intubation	4%	6%	9%	0.28
Intubation in delivery room or NICU	90%	82%	61%	<0.001
Surfactant	78%	71%	52%	<0.001
Pneumothorax	8%	13%	10%	0.58

In the whole population studied (<35 weeks gestational age, n= 2266), multivariate logistic regression analysis taking into account gestational age and umbilical cord base excess, the rate of delivery room intubation significantly decreased after initiation of recruitment into the SUPPORT trial (odds ratio 0.48, 95% CI 0.37, 0.63, $p < 0.001$).

G. METHOD/PROCEDURES:

Study Design:
We propose a retrospective analysis of the GDB using a before/after design with one cohort of patients born before the date of initiation of the SUPPORT trial in each NRN center 1/02-1/05) and a second cohort of patients after release of the SUPPORT trial results to the end of the current cycle of Neonatal Research Network (05/10-4/11)

Study Population:
Cohorts:
We propose to analyze patients in the NRN GDB born between 1/02-4/11, divided into two successive cohorts. The first cohort includes patients born during a 3-year period preceding the SUPPORT trial (from 01/02-1/05). The second cohort includes patients born after the release of the results of the SUPPORT trial to the NRN centers and the end of the neonatal network (05/10-4/11).

Eligibility and exclusion criteria:
We will use eligibility and exclusion criteria identical to those in the SUPPORT trial with the exception of intent to provide full resuscitation, which is not available from the GDB forms.

Entry criteria: Eligible infants are 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at an NRN center participating in the SUPPORT trial, included in the GDB during the entire study period.

Gestational age strata:
We will analyze the same strata as in the SUPPORT trial: 24 0/7ths weeks to 25 6/7ths weeks and 26 0/7ths weeks to 27 6/7ths weeks.

Study Intervention:
This is a retrospective study with before/after study design comparing preterm infants before the date of initiation of the SUPPORT trial and after the release of the results of the SUPPORT Trial in each participating center.

Primary/Secondary Outcomes:

Primary outcome variables:

1. Clinical practices:
    a. The use of intubation vs. CPAP in delivery room
2. Outcomes:
    a. The incidence of composite of death or BPD at 36 weeks (physiologic definition), i.e., a primary outcome of the SUPPORT trial. The Physiologic Definition of BPD assigns the diagnosis of BPD to any infant who received more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks (Walsh 2003, Walsh 2004).
    b. The incidence of composite of severe ROP (defined as received surgery for ROP or retinal detachment from ROP or death before discharge from the hospital. This outcome is similar but not identical to a primary outcome of the SUPPORT trial.
    c. Mortality rate before discharge
    d. The incidence of severe ROP
    e. The incidence of BPD at 36 weeks (physiologic definition)

Secondary outcome variables:

1. Clinical practices
    a. Institutional oxygen saturation target during the first and the second epochs (obtained by survey of each institution)
    b. Institutional intubation rate
    c. Surfactant administration and number of doses
2. Outcomes:
    a. Delivery room resuscitation: bag and mask ventilation, cardiac compressions, use of code drugs (intravenous epinephrine, endotracheal epinephrine, bicarbonate), Apgar scores at 1 min and 5 min
    b. Temperature within 60 min of birth
    c. Pneumothorax
    d. Pulmonary hemorrhage
    e. Use of corticosteroids for BPD
    f. Duration of ventilation among survivors; duration of CPAP among survivors
    g. FiO2 at 24 hours for infants on CPAP, NIPPV or mechanical ventilation
    h. Duration of oxygen supplementation among survivors
    i. BPD (defined by oxygen requirement at 36 weeks)
    j. Patent Ductus Arteriosus (PDA), PDA requiring indomethacin (or ibuprofen during the second epoch), PDA requiring surgery

k. Severe intraventricular hemorrhage (grade III or IV)
l. Cystic periventricular leukomalacia on cranial ultrasonogram performed closest to 36 weeks postmenstrual age
m. Early onset sepsis and late onset sepsis
n. First day full feeds
o. Weight at 36 weeks
p. Necrotizing enterocolitis (stage 2 or greater)
q. Late-onset septicemia/bacteremia
r. Length of stay
s. Weight at discharge
t. Death under 12 hours
u. Death or mechanical ventilation at day 7
v. Death or BPD (defined by oxygen requirement at 36 weeks)
w. Severe ROP, which for this study we propose to define as ROP surgery or retinal detachment, stage 3 or worse in either eye, and plus disease in either eye~~ROP stage 3 or worse in either eye; plus disease in either eye~~

Additional variables available in the GDB will be collected, including

1. Maternal variables: diabetes, hypertension, singleton vs. multiple pregnancy, prolonged rupture of membranes, antenatal corticosteroids (betamethasone, any/full course), mode of delivery, antibiotics before delivery
2. Neonatal variables: race/ethnicity, gestational age, birth weight, gender, syndromes and/or major malformations

Center-specific information requested by survey for both cohorts:

1. Target oxygen saturation
2. Routine use of prophylactic Indomethacin or Ibuprofen
3. Routine use of caffeine
4. Routine use of I.M. vitamin A if birth weight < 1 kg

Sample Size/Statistical Analysis:

Available sample size:

Data in GDB from January 2002 to December 2004 (DATA AND SAFETY MONITORING PLANS for the SUPPORT Trial) included 4055 infants with a gestational age 24 0/7 – 27 6/7. Assuming 10% exclusions, the first 3-year cohort (1/02-1/05) is estimated to yield approximately 3600 infants for analysis.

The GDB data for 2008 included 1738 inborn infants < 29 weeks gestational age. Therefore we estimate that the second cohort (05/10-4/11) would include approximately 1400 infants.

Sample size calculations will be based on available data [which will be updated with more recent data from the GDB]:

1. year 2000 NRN baseline occurrence data among 24 0/7 to 26 6/7 week gestational age infants of death or survival with BPD (by physiologic definition) at 36 weeks of 67%,

2. year 2000 NRN baseline occurrence data among 24 0/7 to 26 6/7 week gestational age infants of death or threshold retinopathy of 50%
3. years 1993-1997 intubation rate of rate of 80% among extremely low birth weight infants (Shankaran 2002).
4. 2002-05 mortality rate of 21% in extremely low birth weight infants (Morris 2008)
5. 2002-05 severe ROP frequency of 20% in extremely low birth weight infants (Morris 2008)

For the primary outcome variables, we calculated power using chi-square analysis, a 1% level of significance (to account for five co-primary outcomes) and two-tailed tests. The available sample size (n = 5000, 3600 before versus 1400 after SUPPORT) gives a power > 99% to find a significant change in delivery room intubation from 80% to 60%, a change in death or BPD (by physiologic definition) from 50% to 40%, a change in death or severe ROP from 67 to 57%, and a change in severe ROP from 20% to 30%. We will have a power of 94% to detect a change in mortality from 21% to 16%. For multivariate analyses, the sample size is much larger than 10 patients per covariate.

Bivariate analyses:

We will conduct bivariate analyses comparing the before and after cohorts with respect to variables related to mortality and all the outcomes listed above (antenatal steroids, gender, Apgar scores, etc.). Bivariate analyses will be done using chi-square analysis (Mantel-Haenszel chi-square for analyses by gestational age stratum) for categorical variables and using Student t-test or Mann-Whitney test as appropriate for continuous variables.

To test whether releasing the results of the SUPPORT trial impacted mostly centers using infrequent intubation before the trial we will test whether the change in rate of intubation from the first to the second epoch in each center is inversely correlated with intubation rate during the first epoch. For this purpose we will use Spearman rank correlation coefficient or the Pearson correlation coefficient, depending on distribution of the data.

Assuming some centers decided to change their oxygen saturation targets based on the SUPPORT trial results, we will test whether mortality decreased and the rate of ROP increased in centers changing their oxygen saturation target from low (85 to 89% or lower) during the first epoch to high (91 to 95%) during the second epoch, but not in the other centers.

Multivariate analyses:

We will create logistic regression models to predict the primary outcomes based on epoch, center and the prespecified covariates (gestational age, antenatal corticosteroids, gender, singleton vs. multiple, birthweight by 100 g increment) (Tyson 2008).

We will also create models specific for each outcome variable:

- For intubation in the delivery room: Model using as additional variables mode of delivery, and maternal hypertension
- For mortality: Model using as additional covariates Apgar score at 1 minute (Shankaran 2002) and~~,~~ institution-specific oxygen saturation target during that epoch (Carlo 2010); for mortality after NICU admission, model using ~~, and~~ temperature upon admission (Laptook 2007)
- For death or ROP and for ROP: Model using as additional covariate oxygen saturation target in the institution (Carlo 2010)
- For death or BPD and for BPD: Model using as additional covariates ~~intubation in the delivery room,~~ routine center-specific use of caffeine, indomethacin or vitamin A~~,~~ ~~number of doses of surfactant (≤1 vs > 1), FiO2 at 24 hours (≥90% vs < 90%), PDA ligation, indomethacin for PDA, late-onset septicemia/ bacteremia~~ (Schmidt 2006, Schmidt 2007, Tyson 1999~~, Ambalavan 2008, Fanaroff 1998, Clyman 2009~~)

If there are additional variables that differ significantly between the two epochs in bivariate analysis we will also include them as covariates as long as they do or could precede the outcome variable.

We will use survival analysis to compare in-hospital death using a Cox proportional hazards model adjusted for gestational age, antenatal corticosteroids, gender, singleton vs. multiple, birthweight by 100 g increment~~covariates listed above~~.

Limitations:

Before/after study design is limited by confounding variables that may have occurred in addition to the variable of interest. The two cohorts represent different patient populations separated by several years. For this purpose, we will perform logistic regression analyses as described in the previous section on multivariate analyses.

One exclusion criterion used for the SUPPORT trial, i.e., decision made not to provide full resuscitation, is not listed in the GDB baseline form.

The outcome of ROP as defined in the SUPPORT trial (threshold retinopathy, or surgical ophthalmologic intervention, or the use of bevacizumab) is not available in the GDB. For the SUPPORT trial, infants were followed for as long as it took to reach the final ROP outcome. In SUPPORT, most cases of severe ROP were diagnosed by 55 weeks PMA, however, many infants will have left the hospital before this time. In contrast, the outcome of ROP available in the GDB, which would be used in this study is based on data recorded prior to the infant's discharge, transfer, or 120 days of life. Thus, there will be a lot of variability in the length of time any infant is "followed" for the outcome.

Furthermore, the data collected with regard to ROP changed between 2002 and 2006. ~~The definitions of ROP changed between 2002 and 2006.~~ We are proposing for this concept proposal to assess the frequency of severe ROP (defined as ROP surgery or retinal detachment), stage 3 or worse in either eye, and plus disease in either eye.

Some variables cannot be analyzed because they were collected during only one of the two cohorts (e.g., tocolytics, origin of cord blood gas and base deficit).

Consenting:
Patients will be selected from GDB using criteria previously explained. We request a waiver for consent form as this research involves minimal risk to patients and collecting data in the GDB has been pre-approved by the IRB in each institution.

Available Population/compatibility with other ongoing protocols
The population available will be those patients in the GDB, corresponding to patients born between 1/01 and 4/11.
We are not aware of any conflict with other ongoing protocols.

Projected Recruitment Time
Data collection for the proposed study will start in May 2011.

H. RISKS/BENEFITS:
The benefit will be mostly for the society in that there is potential quality improvement of patient care in NICU. The risk is minimal and included accidental disclosure of medical information which is unlikely.

I. BUDGET:
Cost for access to GDB and SUPPORT database and statistical analysis

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Retinopathy of prematurity and actual oxygen saturations: A secondary protocol of the SUPPORT Trial

Statement of the Problem

Retinopathy of prematurity (ROP) is an important cause of blindness and other visual disabilities in preterm infants. Its occurrence is indirectly proportional to gestational age. High oxygen saturation levels have been associated with increased risk of retinopathy. In the SUPPORT Trial it was found that severe ROP among survivors was decreased in the lower oxygen saturation group (8.6% in the 85 – 89% oxygen saturation group versus 17.9% in the 91-95% oxygen saturation group (RR = 0.52; CI = 0.37, 0.73; $P < 0.001$; number needed to treat = 11)). However, the median oxygen saturation while receiving oxygen supplementation of infants in the two treatment groups overlapped considerably (Figure). The actual median saturation levels were slightly higher than target levels in both treatment groups. In addition, the duration of oxygen supplementation was shorter in the infants in the lower oxygen saturation group.

Thus, there is a need to determine the actual oxygen saturation levels that were associated with ROP. This is very important because the actual oxygen saturation levels achieved differed from the targets aimed for in the SUPPORT Trial. Furthermore, it is possible that the same actual oxygen saturation levels increased the risk for ROP differently in infants at each gestational age from 24 to 27 weeks. It is also likely that the duration of oxygen exposure affects the risk for ROP. This proposed secondary study will test the hypothesis that there is a range of median oxygen saturation levels that increases the risk of severe ROP disproportionately independent of other baselines characteristics. It will also test the

hypothesis that gestational age, duration of oxygen exposure, and center will affect the risk of severe ROP independent of other characteristics.

Background and significance

Despite years of research to reduce ROP, this disease continues to affect many preterm infants. The incidence of retinopathy of prematurity increased with exposure to unrestricted oxygen in preterm infants in randomized controlled trials performed in the 1950s.[1] This resulted in the practice of restricting oxygen supplementation usually to no more than 50% inspired oxygen concentration, which was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of retinopathy of prematurity relative to low normal levels.[3-5] Although a multicenter observational study did not report a significant association between PaO_2 levels and retinopathy[6], a single center cohort study using transcutaneous oxygen monitoring supported an association of increasing risk of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[7]

Pulse oximetry allows clinicians to continuously monitor oxygen saturations and to target levels in a defined range. Associations between lower oxygen saturation targeting and a lower incidence of retinopathy have been reported in recent years. (3-5) In a survey of 144 neonatal intensive care units, the rate of retinal ablation surgery among very low birth weight infants was higher in infants cared for in units that used higher maximum oxygen saturation targets ; these rates were 3.3 % and 1.4%, respectively, for units using 92% or greater, versus below 92% , and 5.6% and 3.1%, respectively, for units using 98% or greater, versus less than 98%).[3] In a retrospective study comparing outcomes at five neonatal intensive care units, the incidence of severe retinopathy requiring ablation therapy was 27% in

units where target saturations were 88 to 98% and only 6% in units where the target was 70 to 90%.[3] In three pre-post design studies, implementation of a policy of oxygen saturation targeting of approximately 83 to 95% was associated with a substantial reduction in retinopathy compared to the period before the policy, but actual oxygen saturations achieved, mortality, and neurodevelopmental outcomes were not reported.[4, 8, 9] While data from these studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease retinopathy of prematurity, concerns remain about the safety of low oxygen saturation targets.

While the SUPPORT Trial resulted in lower ROP rates in the lower oxygen saturation group, there needs to be more research to determine the specific levels of oxygen saturation that led to the reduction in ROP. This is the primary goal of this secondary study.

Study Design

This will be a secondary analysis of the data from the oxygen saturation intervention group of the SUPPORT Trial. The primary hypothesis will be that there is a range of median oxygen saturation (during oxygen supplementation) that increases the risk of severe ROP (as defined in SUPPORT) disproportionately. The secondary hypothesis will be that gestational age, duration of oxygen exposure, and center differences will affect the risk of severe ROP. In addition, we will test the hypothesis that center differences in the incidences of severe ROP are explained in part by differences in oxygen saturations achieved.

A similar analysis will be proposed once the 18-22 month data are available. For this analysis, blindness and other visual outcomes will be tested in the same way to determine the variables associated with

blindness. However, this will be the subject of another protocol and is only mentioned here to be comprehensive.

Study Population

The study population will be the same as that in the SUPPORT Trial.

Statistical Considerations

The primary analysis will test the impact of median oxygen saturation and the duration of exposure to supplemental oxygen on the incidence of severe ROP using robust Poisson regression implemented in a Generalized Estimating Equation (GEE) model. The model will include covariates for center and gestational age stratum, and will adjust for familial clustering. We will also use multivariate methods such as discriminant analysis to explore the relationship between time spent in various oxygen saturation ranges and the incidence of severe ROP. Because of the competing outcome of death, these analyses will also be done with death/ROP and death as the outcome measure.

Costs

The major cost will be the RTI time in finalizing the analysis plan and doing the data analysis.

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Table 1. Effect of Retinopathy Adjudication for Low vs. High Oxygen Saturation Target Groups

Characteristic	Lower Saturation Group (N=654) n/N (%)	Higher Saturation Group (N=662) n/N (%)	Relative Risk for Low SpO_2 vs. High SpO_2 (95% CI)	Adjusted P value
Severe retinopathy/death without adjudication result	171/605 (28.3)	198/616 (32.1)	0.9 (0.76, 1.06)	0.205
Severe retinopathy among survivors without adjudication result	41/475 (8.6)	91/509 (17.9)	0.52 (0.37, 0.73)	<0.001
Severe retinopathy/death with adjudication result (majority rule)*	171/642 (26.6)	198/656 (30.2)	0.91 (0.77, 1.07)	0.253
Severe retinopathy among survivors without adjudication result (majority rule)*	41/512 (8.0)	91/549 (16.6)	0.52 (0.37, 0.73)	<0.001
Severe retinopathy/death with adjudication result ('unknown' set to severe retinopathy =Y)†	183/654 (28.0)	204/662 (30.8)	0.93 (0.79, 1.1)	0.412
Severe retinopathy among survivors without adjudication result ('unknown' set to severe retinopathy =Y)†	53/524 (10.1)	97/555 (17.5)	0.62 (0.45, 0.84)	0.002

Relative risks are adjusted for gestational age stratification, center, and familial clustering;

*Majority rule: If two reviewers determined that the infant 'Probably never had retinopathy that met criteria for severe retinopathy intervention (laser/cryo) in either eye' then retinopathy=N; If two reviewers determined that 'There is no way to know if severe retinopathy criteria may have been met' then severe retinopathy=missing.

†'Unknown' set to severe retinopathy=Y: If two reviewers determined that the infant 'Probably never had retinopathy that met criteria for severe retinopathy intervention (laser/cryo) in either eye' then

retinopathy=N; if two reviewers determined that 'There is no way to know if severe retinopathy criteria may have been met' then severe retinopathy=Y.

From: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]; Jon E Tyson
Subject: Fw: SUPPORT Trial Concurrent Enrollment with Cycled Light
Date: Monday, June 06, 2005 11:38:00 AM
Attachments: Strat schema with SUPPORT.doc

Dear Rose and Jon,
I hopes this takes care of this issue. Thank you both for your help in getting this resolved.
Ron

----- Forwarded by Ronald N Goldberg/Pediatrics/mc/Duke on 06/06/2005 11:36 AM -----

Debra Brandon <brand005@mc.duke.edu>

06/06/2005 11:35 AM

To: "Ronald N Goldberg" <goldb008@mc.duke.edu>
cc: Michael Cotten <cotte010@mc.duke.edu>
Subject: SUPPORT Trial Concurrent Enrollment with Cycled Light

Ron,

I feel confident that the proposed randomization schedule will protect not only the SUPPORT trial, but also the cycled light study.

Please let me know if we can proceed.

Sincerely,

Debbie Brandon PhD, RN, CCNS
Assistant Professor and Neonatal Specialty Director
Duke University School of Nursing
Neonatal Clinical Nurse Specialist
Duke University Hospital
Box 3322 DUMC
Durham, NC 27710
919-681-3813 voicemail
919-970(b) (6)pager
919-668-6120 fax

Stratification Schema for Dual Enrollment of Cycled Light and SUPPORT Trials

The stratified, randomized design for dually enrolled babies is given in Figure 1 below. Babies enrolled in the SUPPORT study will have been stratified into the four SUPPORT study strata [A-D, based on the color of the pulse oximeter and the unblinded respiratory treatment group] before they are enrolled in the Cycled Light Study At this point, we will stratify by gestational age (< 26 weeks vs. 26 or more weeks) resulting in the eight SUPPORT by gestational age strata. Within each of these eight cells, we will randomize into two cycled light groups (early cycled light: at 28 weeks or late cycled light: at 36 weeks). We plan on enrolling an additional 70 infants in the Cycled Light study.

Figure 1: Stratified Design for Babies Enrolled in the Support and the Cycled Light Studies.

INTUBATION							
[A] High O2 (color)				[B] Low O2 (color)			
(1) Gestational age < 26 weeks		*(2)* Gestational age >= 26 weeks		*(3)* Gestational age < 26 weeks		*(4)* Gestational age >= 26 weeks	
cycled light: yes	cycled light no	cycled light yes	cycled light no	cycled light yes	cycled light no	cycled light yes	cycled light no
NASAL CPAP							
[C] High O2 (color)				[D] Low O2 (color)			
(5) Gestational age < 26 weeks		*(6)* Gestational age >= 26 weeks		*(7)* Gestational age < 26 weeks		*(8)* Gestational age >= 26 weeks	
cycled light: yes	cycled light no	cycled light: yes	cycled light no	cycled light: yes	cycled light no	cycled light: yes	cycled light no

From: Hastings, Betty J.
To: wrich@ucsd.edu
Cc: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; ahensman@wihri.org; mbball@leland.stanford.edu; Zaterka-Baxter, Kristin
Subject: RE: Supp 11
Date: Friday, June 03, 2005 8:20:01 AM

Wade,
I think it would be best NOT to make any changes to the forms or manual at this time. I know we talked about it but there are just too many unanswered questions right now. How about if I ask the coordinators to bring the latest version of the manual, forms and their questions for discussion during the 4-5pm time that has been set aside to discuss the trial? Hopefully everyone will then be on the same page and we can make all revisions and send these out again.
How does that sound to you?
Thanks.
Betty

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, June 02, 2005 5:50 PM
To: 'M. Bethany Ball'
Cc: Hastings, Betty J.; ahensman@wihri.org; higginsr@mail.nih.gov; nfiner@ucsd.edu
Subject: RE: Supp 11

Bethany,
Thank you for your thoughtful comments:

The use of oxygen for this trial after 14 days is truly significant only as a yes or no question. We are currently asking if the baby is on any type of support and what his most frequent FiO2 is. Dr. Finer is ok with just defining the oxygen question as "Supplemental oxygen? Yes/No".

The operative sentence in this is "Dr. Finer is ok with just defining the oxygen question as "Supplemental oxygen? Yes/No"." If that truly is all that you want to know after day 14, then create a form with fields for study days 15-85 with supplemental oxygen Y/N with no other data collected (we would stop data collection at 36 wks). HOWEVER, you will be using this form to figure out what's going on with the child when you look at the PO data so I think you should have a field for vent/CPAP Yes/No as well.
I apologize that this was not made clear. I did not mean to infer that the Yes/No was in place of support AND FiO2, but only that it would be used in place of a specific FiO2. The highest level of support would still be included.

I proposed increasing the duration definition to 8 hours continuous hours. This would eliminate the back and forth problems, and would mean less chance of having to put the oximeter on after 4 hours in the middle of the night.
You seem to have combined the idea of reporting the use of supplemental oxygen with the re-application of the pulse ox. The protocol states that if the child goes back to supplemental oxygen before 36 weeks he/she is returned to an appropriate study PO. There's nothing in there about hours of oxygen before going back on the study PO and I recommend that you refrain from changing the protocol at this juncture.
I think you will want to know if the child should have been on a study PO on each day so it really doesn't make sense to have a duration definition at all. This is a problem with the new version of the SUPP05 as well. I could have a child on nasal cannula

oxygen for 7.5 hours a day and you would only be able to infer that there was supplemental oxygen being given when you looked at the pulse ox data. What if the child was in room air and we forgot to take the PO off after 72 hours? You could end up with several days of PO data where you inferred the child was getting oxygen and that we were happily violating the protocol with all those saturations of 99. Similarly, we could accidentally take the pulse ox off early and you wouldn't have any way of knowing. In addition, by using a duration definition you lose the ability to audit the data by comparing it with the NG07.

The intent here is to eliminate putting infant on and off the oximeter for feedings and transient changes in oxygen, which are occuring frequently at network sites.

Also on the SUPP05, the section for recording nasal cannula has a field for FiO2. What you actually want there is the blend or concentration of oxygen provided since the fraction of inspired oxygen can only be estimated when nasal cannula is used. Asking for FiO2 opens the door for someone to decide to calculate the value, particularly since guesstimating the FiO2 has been used for Benchmarking and is now being used for the physiologic challenge in the GDB. I suggest you use "% oxygen" and state in the manual that you want the blend and flow provided, not a calculation of the FiO2.
I agree.

I want to remind you that you haven't addressed the problem with the second technical memo.
It states that the child should remain on the study PO until, "... has been **without support** (HFV, CV, CPAP, Nasal Cannula) **for 72 hours**." In fact, since we know that one center uses hoods and another floods isolettes for O2 delivery, the criteria for removal of the study PO should be something like, "the child should be in room air and without support for 72 hours". Otherwise, we run the risk of kids coming off study POs while getting supplemental O2 via rogue sources.
This has been addressed, but not yet made public, as I was waiting for folks comments re: the form so Betty could make all the changes at once.
One minor issue, please remove the field for study day in the header of the SUPP11.
Done. Again, just not published yet.
Best regards,
Beth

X-Sieve: CMU Sieve 2.2
Subject: Supp 11
Date: Thu, 2 Jun 2005 12:18:34 -0400
Thread-Topic: Supp 11
Thread-Index: AcVnjrdZ/RuZ66GbSp2B7lbVrohIDg==
X-Priority: 1
Priority: Urgent
Importance: high

From: "Hastings, Betty J." <bkh@rti.org>

From Wade Rich:

Dear Coordinators:

I have fielded a suggestion for the Supp11 form which will make data collection easier, and I need you to let me know what you think prior to the Network meeting in a couple of weeks. We are supposed to be meeting at some time during those two days, but I do not know if it will be before the SUPP subcommittee meeting.

The use of oxygen for this trial after 14 days is truly significant only as a yes or no question. We are currently asking if the baby is on any type of support and what his most frequent FiO2 is. Dr. Finer is ok with just defining the oxygen question

as "Supplemental oxygen? Yes/No". This would simplify things. I proposed increasing the duration definition to 8 hours continuous hours. This would eliminate the back and forth problems, and would mean less chance of having to put the oximeter on after 4 hours in the middle of the night.

Neil is even willing to consider 12 hours. If a baby is on support for more than 8 continuous hours but oxygen for less than 8, you would answer the support question Yes and the oxygen question No.

Let me know if you guys think this is workable. I want your opinions, not your PIs. They will get their chance at the subcommittee meeting.
PLEASE RESPOND TO WADE BY JUNE 10TH!!

Thanks,
Wade

Wade Rich, BS, RRT-NPS
Clinical Research Coordinator
Division of Neonatology
UCSD Medical Center
200 W Arbor Dr
San Diego, CAÊ 92103-8774
619-543-5375
pgr 290(b) (6)

Betty Hastings

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Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

From: Susan Hintz
To: Duara, Shahnaz
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hintz MRI secondary
Date: Thursday, June 02, 2005 1:44:26 PM

Shahnaz,

I will be at the Steering committee meeting - should I just discuss it then, or do you think I should send an email? I might just include it in the email I send with the forms/manual -

Susan

>That's great - I would circulate this information to all the PIs, as we
>are embarking into a new area of collaboration. It will help everyone
>when talking to their MRI centers and radiologists.
>
>Shahnaz
>
>-----Original Message-----
>From: Susan Hintz [mailto:srhintz@stanford.edu]
>Sent: Thursday, June 02, 2005 11:40 AM
>To: Higgins, Rosemary (NIH/NICHD)
>Cc: Duara, Shahnaz
>Subject: RE: Hintz MRI secondary
>
>
>Hi Shahnaz,
>
>We need two central readers for MRIs - thus, one more is needed. My
>understanding is that, if a radiologist is interested in being a
>central reader, his or her CV must be submitted to the data center,
>the SUPPORT subcommittee and I would review the CVs to assure
>appropriate expertise, and then a choice would be made. Monetary
>compensation for central readers is arranged through the data center
>- I am not sure how much the premie iNO US central readers received,
>but maybe you could ask Ken or Rose. With respect to authorship, it
>would depend entirely on the level of contribution to the analysis in
>question. I would not expect the central readers to be authors on,
>for instance, the neurodevelopmental outcomes paper. However, they
>might be co-authors on a descriptive paper of MRI findings in this
>population. Also, an ancillary or request for additional analysis
>could certainly be made if there is a specific question you/your
>radiologist would be interested in looking at -
>
>Does that help? Call me if you want to talk more about it.
>
>Susan
>Susan R. Hintz, M.D.
>Assistant Professor of Pediatrics
>Division of Neonatal and Developmental Medicine
>Stanford University School of Medicine
>750 Welch Road, Suite 315
>Palo Alto, CA 94304

>ph: 650-723-5711
>fax: 650-725-8351
>
>>Shahnaz,
>>I am unsure so am copying Susan on the email to clarify this point.
>>Thanks Rose
>>-----Original Message-----
>>From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
>>Sent: Wednesday, June 01, 2005 4:28 PM
>>To: Higgins, Rosemary (NIH/NICHD)
>>Subject: RE: Hintz MRI secondary
>>
>>Hi Rose,
>>
>>I wasn't thinking of an ancillary. What I was wondering was if site
>>radiologists were interested in sharing the task of 'central reader',
>>as Susan mentions in the protocol, what has the discussion of how those
>
>>readers will be rewarded? I'm getting my ducks in a row before I speak
>>to our radiologists, just in case one of them is interested in doing
>>more than providing fee for service.
>>
>>Thanks
>>Shahnaz
>>
>>-----Original Message-----
>>From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
>>Sent: Wednesday, June 01, 2005 1:41 PM
>>To: Duara, Shahnaz
>>Subject: RE: Hintz MRI secondary
>>
>>
>>Shahnaz,
>>Authorship would be determined by an authorship plan based on specific
>>contribution to the study. If there is an ancillary to the secondary,
>>I would encourage you and your colleagues to ring it forward. As far
>>as capitation is concerned, we are recommending to Grants management
>>that the total for patient with a completed study (enrollment and head
>>US in first 14 days, followed by MRI and head US at 36 weeks) would be
>>approximately $1300. Let me know if you have other questions. Thanks
>>Rose
>>
>>
>>-----Original Message-----
>>From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
>>Sent: Wednesday, June 01, 2005 12:05 PM
>>To: Higgins, Rosemary (NIH/NICHD)
>>Subject: Hintz MRI secondary
>>
>>Hi Rose,
>>
>>I am trying to set up some internal discussions with the research MRI
>>folks at Miami. With the central reader planned, is there any
>>opportunity for authorship if someone locally is interested in
>>participating? Also, what is te final rate of capitation that was
>>decided upon for the MRIs?
>>

>>Thanks in advance
>>Shahnaz
>
>
>--

From: Roy Heyne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: Pulmonary Outcomes for Support--2 more articles
Date: Thursday, June 02, 2005 12:19:55 PM
Attachments: PulmOutcomeFollowon_comments.doc

Rose, FYI.

>>> Roy Heyne 06/02/05 7:42 AM >>>
just ran across two interesting articles from the UK assessing accuracy of parents' interpretations of children's respiratory symptoms: Cane and McKenzie "Parents interpretations of children's respiratory symptoms on video" Arch Dis Child2001; 84:31-34 and Elphick et. al. "Survey of respiratory sounds in infants" Arch Dis Child 2001; 84:35-39.

>>> Roy Heyne 05/31/05 7:46 AM >>>
Janet just reminded me of two more points, which I did not include in my comments last Friday, though I did raise one at our meeting in D.C.: 1) We need to provide some incentive for participation, since this will involve additional time and trouble on the part of the family; 2) as in the case of the PCV7 study, we need the flexibility to be able to enroll and obtain the baseline questionnaire within 2-4 weeks after discharge (at our first follow-up visit), rather than prior to discharge, which latter is a more challenging time to try to connect with our families).

>>> Roy Heyne 05/27/05 5:41 PM >>>
One other interesting article that addresses the llimited accuracy of reported wheezing was published last year in Arch Dis Child 89:540-543 by Lowe et. al.

>>> Roy Heyne 05/27/05 4:05 PM >>>
Rose, I am attaching a Word document with my comments regarding the proposed SUPPORT pulmonary follow-on study. LEt me know if you have questions. Thanks for considering.

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 05/23/05 11:25 AM >>>
Janet
Thanks so much for getting back to us. I believe patient (b) (6) originated from the Cincinnati site. Is this correct?
Thanks again for the attention to the details!
Rose

-----Original Message-----
From: JANET MORGAN [mailto:JANET.MORGAN@childrens.com]
Sent: Monday, May 23, 2005 12:00 PM
To: Roy Heyne
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: Re: Fwd:

Dr. Heyne,
We have completed clients # (b) (6), info has not yet been entered. Clients (b) (6) are scheduled in May and June. Clients (b) (6) are for various reason not scheduled yet. Two of these are out of town and we are tring hard to get some follow-up..not sure we will be successful and the other we are having trouble locating.
Janet

>>> Roy Heyne 5/20/2005 11:35:48 AM >>>
Could you please check these out. Thanks.

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 05/20/05 11:22 AM >>>

Hi,

We appreciate the hard work and dedication of all the sites in their participation in the Preemie iNO trial. As you know, a crucial component of this trial is neurodevelopmental outcome at 18-22 months corrected age. To assure the best possible follow-up, we ask you to look into the following follow-up issues, and respond to concerns as soon as possible. Please note that, even if the follow-up window has "closed", the neurodevelopmental follow-up visit should still be done.

Preemie iNO Surviving Infants Not Followed Up

Mother First Name	Mother Last Name	Follow-up Study Start Date	Follow-up Study End Date	Gestational Birth Age Weeks	Center ID	Study Name
4:Univ. of Texas Dallas	(b) (6) [redacted]			32		Main
PR	THO	07/10/04	11/23/04			
	(b) (6) [redacted]			31		Main
SMP		12/31/04	05/16/05			
	(b) (6) [redacted]			28		Main
AC		05/04/05	09/17/05			
	(b) (6) [redacted]			27		Main
LMV		05/19/05	10/02/05			
	(b) (6) [redacted]			32		Main
MR		04/19/05	09/02/05			

(b) (6) [redacted] 28
Main
LLS 05/27/05 10/10/05

(b) (6) [redacted] 31
Large
TL 05/22/05 10/05/05

Please send us the status including appointment date for the children listed
above.

For patients who are truly lost, we recommend using the following web sites
to search for their whereabouts (some of these were successfully used to
locate patients in previous network trials):
www.555-1212.com
<file:///C:\Documents%20and%20Settings\higginsr\Local%20Settings\Temporary%20Internet%20Files\OLKC2\www.555-1212.com> (cost $20 for 100 lookups)

www.USA-people-search.com
<http://www.USA-people-search.com%20the%20cost%20$9-95> The cost for addresses, phone # birthdays searched is $9-95

www.anywho.com <http://www.anywho.com> . This is free but addresses may not
be current

www.peopledata.com <http://www.peopledata.com> . this is $10 for address

www.find.intelius.com <http://www.find.intelius.com> use search by ss# for
$49.95

Thank you for your ongoing commitment!

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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NICHD, NIH

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301-496-3790 (FAX)

higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

SUPPORT Trial Pulmonary Outcomes Follow On Study

Comments by R. Heyne, M.D. Dallas 5/27/05

As I indicated at the recent Follow-up PI meeting in Washington, I think a study to follow pulmonary outcomes beyond the nursery is definitely indicated in this population; however, I have a number of concerns regarding the study design, both with regards to the outcome measures chosen, the method of ascertainment, and thus the interpretation and validity of the outcome data the study will produce.

1) Definition of Outcomes: As pointed out in the Background and Methods sections of the protocol, a variety of parent questionnaires have been used in prospective cohort studies to identify and quantify, and/or otherwise characterize, lower respiratory symptoms and/or disease in the first 2-3 years of life. However, the extent of published validation of various survey questions in cited references 48-54 is less clear. Koopman et. al. (reference 43 in the protocol) reviewed all these cited studies, along with several more, and still raised some of the same questions/concerns I have regarding the accuracy of various reported symptoms.
    a. This is especially true in the case of wheezing, which is the most commonly studied, yet probably most problematic, reported symptom.
        i. Members of non-wheezing families do not necessarily recognize a wheeze properly, and upper respiratory noises are difficult to differentiate from wheeze. "Whistling" is not much more helpful.
        ii. Even when families bring the child in to the office for possible "asthma" symptoms, it may not be as simple as it seems to help them precisely recognize/differentiate wheezing. It may take experience over time with variations on the theme, depending on how "classical" the child's presentation is, before they develop a more sensitive/specific ability.
        iii. Many languages do not have a precise (specific) equivalent for wheezing; and there can be interesting dialect/colloquial variants.
        iv. Many of our Spanish families report "ronco," which is almost as non-specific as "gripe." And not all are aware of other terms, such as "jadeo" or "chiflido."
        v. It is not clear that any of the reported surveys have been validated in different languages, Spanish or otherwise.
        vi. Trying to define/differentiate wheezing for the first time over the phone can be challenging and time-consuming, even for someone who knows the family/child.
    b. Even something as common, and seemingly simple, as a "cold" means different things to different people, and may include everything from a bout of allergic rhinitis to non-specific rhinorhea to a full-blown viral upper respiratory infection with fever, etc.
    c. Cough is less equivocal per se, but precisely characterizing its nature and frequency is more of a challenge. Moreover, though we all recognize "cough variant asthma," the prognostic value/significance of cough in infancy for later asthma is less clear.

d. Asking about a history of physician-diagnosed "asthma" may also over or under state the case, for several reasons:
    i. Physicians may variously apply the term asthma to one or more bouts of "reactive airway disease."
    ii. As Brooks et. al. (protocol reference #14) point out, "physicians may be more or less likely to attribute wheezing in a LBW child to 'asthma' depending on their belief that wheezing is expected in children born prematurely."
    iii. In the case of ELBW infants, outpatient physicians are more likely to carry on with a diagnosis of BPD or CLD of prematurity, rather than introduce the new term of "asthma" (or RAD), which can have other connotations to parents.
    iv. Without some further information concerning quality and quantity of symptoms, direction and magnitude of possible bias is hard to accurately assess.
e. Possible solutions would include one or more of the following:
    i. Some further definition/explanation of terms for families at the outset of the study, in oral and/or written form;
    ii. Some reminder/reinforcement during the phone interview, which would lengthen an already lengthy interview;
    iii. Some further validation through chart audit, which would be much more time consuming and much less feasible where primary care is not centralized.

2) Ascertainment of Outcomes
    a. For children who have had more than an isolated bout or two of one or more of the symptoms in the questionnaire, which necessitates answering another 4-9 questions for each leading positive symptom, the questionnaire can turn into a very long phone interview.
    b. Precision of recall of number of office visits, never mind dates of such, is going to be progressively limited, the greater the number of visits, even for periods as short as 6 months.
    c. Even for more dramatic events such as ER and hospitalization, precision of date recall is going to be limited.
    d. Koopman et. al. have suggested that recall bias may influence results.
    e. Though a centralized approach to phone interviews may have the benefits listed, it would not succeed with our families for the following reasons:
        i. A significant percentage of our families are not U.S. citizens, and would be very wary of anyone they have not met calling them, even if this was explained ahead of time.
        ii. Central staff do not have the same rapport or familiarity with the families that local study staff have.
        iii. Additional tracking/contacts by central staff would likely be more counterproductive than synergistic.

3) Additional Questionnaire Issues: Appendix B&C
    a. Questions 4a-j

   i. Question b., as a., may refer to more than one episode of wheezing, some of which may not have been associated with colds, whereas others were. (As noted above, "colds" is not defined.)
   ii. Question g. does not define "attacks"
b. Questions 6a-j
   i. Question b sounds as if it is referring to a single or "prototypical" episode, whereas both 6 (a) and b could well refer to multiple different types of episodes.
c. Questions 7a-f
   i. Questions e-f ask about the "past year" whereas the interval should only be 6 months for the 6, 12, and 18 month surveys.
d. Questions 8a-d
   i. Question a. appears to lump "any wheezing illness....not due to asthma" along with bronchiolitis. Not sure where BPD/CLD or bronchitis fit in to this equation.
e. Questions 11a-d
   i. Without knowing basis for diagnosis of pneumonia (exam +/- CXR +/- WBC), viral vs. bacterial, not sure what we can make of this history. Might at least want to ask about antibiotics and hospitalization.

From:	Wally Carlo, M.D.
To:	nfiner@ucsd.edu; Abbot Laptook
Cc:	Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; Higgins, Rosemary (NIH/NICHD) [E]; Ken Poole; Michele; Shahnaz Duara; Wade Rich; Wally Carlo
Subject:	RE: Feedback on pulse oximeter data
Date:	Tuesday, May 31, 2005 1:44:54 PM

We collect data on whether they are on oxygen. wally

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, May 31, 2005 12:42 PM
To: 'Abbot Laptook'
Cc: Wally Carlo, M.D.; 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
Subject: RE: Feedback on pulse oximeter data

Abbot
We agree. The question is how much analysis we want for now, and the decision to also monitor while on RA and Hi flow cannula, used at 75% of the sites.
We will discuss at the next Network Meeting and I will discuss with RTI.
See you in 2 weeks
Neil

From: Abbot Laptook [mailto:ALaptook@WIHRI.org]
Sent: Tuesday, May 31, 2005 8:14 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu
Cc: HigginsR@mail.nih.gov; Angelita Hensman
Subject: FW: Feedback on pulse oximeter data

Neil, Wade
I have reviewed the initial feedback of the pulse oximeter downloads and I am wondering how these will be interpreted if one does not know the inspired FiO2. In the absence of knowing the FiO2, do we interpret time with O2 sats above the desired range as poor control or infants who are on room air but remain on a pulse oximeter due to intermittent desaturation episodes or use of CPAP etc? This does get back to the issues raised at the last network meeting and I am still unclear that I understand the processing of data when infants are not continually in oxygen. Intermittent recording of FiO2 is really insufficient. Abbot

---

From: Angelita Hensman
Sent: Tuesday, May 31, 2005 10:09 AM
To: Abbot Laptook
Subject: FW: Feedback on pulse oximeter data

Did you get this?
Angelita

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Tuesday, May 31, 2005 9:41 AM
To: Angelita Hensman
Subject: FW: Feedback on pulse oximeter data

Angelita,
Here is what we last got. We have been promised a monthly update by RTI. This should have gone out to
all of the PIs from Neil. It is not corrected for R/A.

Wade

From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Friday, May 27, 2005 1:55 PM
To: Hastings, Betty J.; Schaefer, Scott E.
Cc: wade rich
Subject: Feedback on pulse oximeter data

Hi Betty and Scott,

Can we get some feedback on pulse oximeter data (how often we are in range) on a regular basis from the data center? We have done 13 downloads to date on 8 patients.

Thanks
Angelita

From: Higgins, Rosemary (NIH/NICHD)
To: Stevens, Timothy
Cc: Phelps, Dale
Subject: FW: Pulmonary Outcomes for Support
Date: Tuesday, May 31, 2005 8:54:00 AM
Attachments: PulmOutcomeFollowon_comments.doc

Tim
Here are a few more suggestions from Roy for the pulmonary outcomes protocol. I think we need to work on a new budget - one that considers the sites doing the questionnaires - probably will take 2-3 hrs/per group. Can you do this?
Thanks
Rose

-----Original Message-----
From: Roy Heyne [mailto:Roy.Heyne@UTSouthwestern.edu]
Sent: Tuesday, May 31, 2005 8:47 AM
To: Higgins, Rosemary (NIH/NICHD)
Cc: JANET MORGAN; BVohr@WIHRI.org
Subject: Fwd: Pulmonary Outcomes for Support

Janet just reminded me of two more points, which I did not include in my comments last Friday, though I did raise one at our meeting in D.C.: 1) We need to provide some incentive for participation, since this will involve additional time and trouble on the part of the family; 2) as in the case of the PCV7 study, we need the flexibility to be able to enroll and obtain the baseline questionnaire within 2-4 weeks after discharge (at our first follow-up visit), rather than prior to discharge, which latter is a more challenging time to try to connect with our families).

>>> Roy Heyne 05/27/05 5:41 PM >>>
One other interesting article that addresses the llimited accuracy of reported wheezing was published last year in Arch Dis Child 89:540-543 by Lowe et. al.

>>> Roy Heyne 05/27/05 4:05 PM >>>
Rose, I am attaching a Word document with my comments regarding the proposed SUPPORT pulmonary follow-on study. LEt me know if you have questions. Thanks for considering.

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 05/23/05 11:25 AM >>>
Janet
Thanks so much for getting back to us. I believe patient (b) (6) originated from the Cincinnati site. Is this correct?
Thanks again for the attention to the details!
Rose

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Sent: Monday, May 23, 2005 12:00 PM
To: Roy Heyne
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: Re: Fwd:

Dr. Heyne,
We have completed clients # (b) (6), info has not yet been entered. Clients (b) (6) are scheduled in May and June. Clients (b) (6) are for various reason not scheduled yet. Two of these are out of town and we are tring hard to get some follow-up..not sure we will be successful and the other we are having trouble

locating.
Janet

>>> Roy Heyne 5/20/2005 11:35:48 AM >>>
Could you please check these out. Thanks.

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 05/20/05 11:22 AM >>>

Hi,

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www.USA-people-search.com
<http://www.USA-people-search.com%20the%20cost%20$9-95> The cost for addresses, phone # birthdays searched is $9-95

www.anywho.com <http://www.anywho.com> . This is free but addresses may not
be current

www.peopledata.com <http://www.peopledata.com> . this is $10 for address

www.find.intelius.com <http://www.find.intelius.com> use search by ss# for
$49.95

Thank you for your ongoing commitment!

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

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301-496-3790 (FAX)

higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

SUPPORT Trial Pulmonary Outcomes Follow On Study

Comments by R. Heyne, M.D. Dallas 5/27/05

As I indicated at the recent Follow-up PI meeting in Washington, I think a study to follow pulmonary outcomes beyond the nursery is definitely indicated in this population; however, I have a number of concerns regarding the study design, both with regards to the outcome measures chosen, the method of ascertainment, and thus the interpretation and validity of the outcome data the study will produce.

1) Definition of Outcomes: As pointed out in the Background and Methods sections of the protocol, a variety of parent questionnaires have been used in prospective cohort studies to identify and quantify, and/or otherwise characterize, lower respiratory symptoms and/or disease in the first 2-3 years of life. However, the extent of published validation of various survey questions in cited references 48-54 is less clear. Koopman et. al. (reference 43 in the protocol) reviewed all these cited studies, along with several more, and still raised some of the same questions/concerns I have regarding the accuracy of various reported symptoms.
    a. This is especially true in the case of wheezing, which is the most commonly studied, yet probably most problematic, reported symptom.
        i. Members of non-wheezing families do not necessarily recognize a wheeze properly, and upper respiratory noises are difficult to differentiate from wheeze. "Whistling" is not much more helpful.
        ii. Even when families bring the child in to the office for possible "asthma" symptoms, it may not be as simple as it seems to help them precisely recognize/differentiate wheezing. It may take experience over time with variations on the theme, depending on how "classical" the child's presentation is, before they develop a more sensitive/specific ability.
        iii. Many languages do not have a precise (specific) equivalent for wheezing; and there can be interesting dialect/colloquial variants.
        iv. Many of our Spanish families report "ronco," which is almost as non-specific as "gripe." And not all are aware of other terms, such as "jadeo" or "chiflido."
        v. It is not clear that any of the reported surveys have been validated in different languages, Spanish or otherwise.
        vi. Trying to define/differentiate wheezing for the first time over the phone can be challenging and time-consuming, even for someone who knows the family/child.
    b. Even something as common, and seemingly simple, as a "cold" means different things to different people, and may include everything from a bout of allergic rhinitis to non-specific rhinorhea to a full-blown viral upper respiratory infection with fever, etc.
    c. Cough is less equivocal per se, but precisely characterizing its nature and frequency is more of a challenge. Moreover, though we all recognize "cough variant asthma," the prognostic value/significance of cough in infancy for later asthma is less clear.

d. Asking about a history of physician-diagnosed "asthma" may also over or under state the case, for several reasons:
    i. Physicians may variously apply the term asthma to one or more bouts of "reactive airway disease."
    ii. As Brooks et. al. (protocol reference #14) point out, "physicians may be more or less likely to attribute wheezing in a LBW child to 'asthma' depending on their belief that wheezing is expected in children born prematurely."
    iii. In the case of ELBW infants, outpatient physicians are more likely to carry on with a diagnosis of BPD or CLD of prematurity, rather than introduce the new term of "asthma" (or RAD), which can have other connotations to parents.
    iv. Without some further information concerning quality and quantity of symptoms, direction and magnitude of possible bias is hard to accurately assess.
e. Possible solutions would include one or more of the following:
    i. Some further definition/explanation of terms for families at the outset of the study, in oral and/or written form;
    ii. Some reminder/reinforcement during the phone interview, which would lengthen an already lengthy interview;
    iii. Some further validation through chart audit, which would be much more time consuming and much less feasible where primary care is not centralized.

2) Ascertainment of Outcomes
    a. For children who have had more than an isolated bout or two of one or more of the symptoms in the questionnaire, which necessitates answering another 4-9 questions for each leading positive symptom, the questionnaire can turn into a very long phone interview.
    b. Precision of recall of number of office visits, never mind dates of such, is going to be progressively limited, the greater the number of visits, even for periods as short as 6 months.
    c. Even for more dramatic events such as ER and hospitalization, precision of date recall is going to be limited.
    d. Koopman et. al. have suggested that recall bias may influence results.
    e. Though a centralized approach to phone interviews may have the benefits listed, it would not succeed with our families for the following reasons:
        i. A significant percentage of our families are not U.S. citizens, and would be very wary of anyone they have not met calling them, even if this was explained ahead of time.
        ii. Central staff do not have the same rapport or familiarity with the families that local study staff have.
        iii. Additional tracking/contacts by central staff would likely be more counterproductive than synergistic.

3) Additional Questionnaire Issues: Appendix B&C
    a. Questions 4a-j

   i. Question b., as a., may refer to more than one episode of wheezing, some of which may not have been associated with colds, whereas others were. (As noted above, "colds" is not defined.)
   ii. Question g. does not define "attacks"
b. Questions 6a-j
   i. Question b sounds as if it is referring to a single or "prototypical" episode, whereas both 6 (a) and b could well refer to multiple different types of episodes.
c. Questions 7a-f
   i. Questions e-f ask about the "past year" whereas the interval should only be 6 months for the 6, 12, and 18 month surveys.
d. Questions 8a-d
   i. Question a. appears to lump "any wheezing illness....not due to asthma" along with bronchiolitis. Not sure where BPD/CLD or bronchitis fit in to this equation.
e. Questions 11a-d
   i. Without knowing basis for diagnosis of pneumonia (exam +/- CXR +/- WBC), viral vs. bacterial, not sure what we can make of this history. Might at least want to ask about antibiotics and hospitalization.

From: Betty Vohr
To: Roy Heyne; Higgins, Rosemary (NIH/NICHD) [E]
Cc: JANET MORGAN
Subject: RE: Pulmonary Outcomes for Support
Date: Monday, May 30, 2005 9:14:48 AM

Thanks so much for your thoughtful comments and review of this area.

From: Roy Heyne [mailto:Roy.Heyne@UTSouthwestern.edu]
Sent: Fri 5/27/2005 5:05 PM
To: higginsr@mail.nih.gov
Cc: JANET MORGAN; Betty Vohr
Subject: Pulmonary Outcomes for Support

Rose, I am attaching a Word document with my comments regarding the proposed SUPPORT pulmonary follow-on study. LEt me know if you have questions. Thanks for considering.

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may not
be current

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higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

From: Barbara Stoll
To: Neil Finer
Cc: Ellen Hale; Higgins, Rosemary (NIH/NICHD) [E]; Susie Buchter
Subject: Re: FW: SUPPORT
Date: Sunday, May 29, 2005 10:32:02 AM

Susie Buchter is the PI for the study.
I will let her respond.
FYI-- another consent this AM
BJS"Neil Finer" <nfiner@ucsd.edu> writes:
>Congratulations
>Welcome aboard.
>Where there any issues around this baby and the protocol??
>Regards, and enjoy the weekend!
>Neil
>
>-----Original Message-----
>From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
>Sent: Friday, May 27, 2005 3:30 PM
>To: 'barbara_stoll@oz.ped.emory.edu'; 'nfiner@ucsd.edu'
>Cc: 'ellen_hale@oz.ped.emory.edu'
>Subject: Re: SUPPORT
>
>Terrific!
>Rose
>----------
>Sent from my BlackBerry Wireless Handheld
>
>
>-----Original Message-----
>From: Barbara Stoll <barbara.stoll@oz.ped.emory.edu>
>To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
>CC: Ellen Hale <ellen.hale@oz.ped.emory.edu>
>Sent: Fri May 27 18:16:02 2005
>Subject: SUPPORT
>
>Susie was in the DR to enter the first baby in the SUPPORT trial--
>randomized to CPAP
>He is 1030 g/27 4/7 weeks and looks great on CPAP-- now about (b) (6) [redacted]!
>BJS
>
>Barbara J. Stoll, MD
>George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
>Medical Director, Children's Healthcare of Atlanta at Egleston
>Office: 404-727-2456 Fax: 404-727-5737
>barbara_stoll@oz.ped.emory.edu
>
>This message is for the designated recipient only and may contain
>privileged or confidential information. If you have received it in error,
>please notify the sender immediately and delete the original.
>

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
Medical Director, Children's Healthcare of Atlanta at Egleston
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

From:	wade rich
To:	"Neil Finer"; "Hastings, Betty J."
Cc:	"Avroy A. Fanaroff, M.D."; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Shahnaz Duara"
Subject:	RE: Pulse oximeter replacement on SUPPORT baby
Date:	Sunday, May 29, 2005 9:41:06 AM

Coordinators do not understand ranges ("at least 8-12 hours.") We said at least 8 hours on the form.
wade

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, May 26, 2005 2:43 PM
To: 'Hastings, Betty J.'
Cc: wrich@ucsd.edu; 'Avroy A. Fanaroff, M.D.'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'
Subject: RE: Pulse oximeter replacement on SUPPORT baby

Hi Betty
I would respond by saying that if the infant does not need oxygen for at least 8-12 hours per day that we should not use the study oximeters, and certainly not for a brief period around feedings..
Wade is traveling so I will copy him and see if he agrees
Any other thoughts?.
Neil

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Thursday, May 26, 2005 7:24 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu
Subject: FW: Pulse oximeter replacement on SUPPORT baby
Importance: High

Neil/Wade,
We need clarification regarding the question below. Thanks very much for your help.
Betty
-----Original Message-----
From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Thursday, May 26, 2005 10:07 AM
To: Hastings, Betty J.
Cc: Abbot Laptook
Subject: Pulse oximeter replacement on SUPPORT baby

Hi Betty,

Another question we need some clarification on:

If the pulse oximeter is d/ced prior to 36 wks GA but the baby subsequently requires oxygen for "feeds only" (prior to 36 wks) does this baby need to go back on the study pulse oximeter?

Thanks
Angelita

From: Roy Heyne
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: JANET MORGAN; BVohr@WIHRI.org
Subject: Fwd: Pulmonary Outcomes for Support
Date: Friday, May 27, 2005 6:42:18 PM
Attachments: PulmOutcomeFollowon_comments.doc

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Comments by R. Heyne, M.D. Dallas 5/27/05

As I indicated at the recent Follow-up PI meeting in Washington, I think a study to follow pulmonary outcomes beyond the nursery is definitely indicated in this population; however, I have a number of concerns regarding the study design, both with regards to the outcome measures chosen, the method of ascertainment, and thus the interpretation and validity of the outcome data the study will produce.

1) Definition of Outcomes: As pointed out in the Background and Methods sections of the protocol, a variety of parent questionnaires have been used in prospective cohort studies to identify and quantify, and/or otherwise characterize, lower respiratory symptoms and/or disease in the first 2-3 years of life. However, the extent of published validation of various survey questions in cited references 48-54 is less clear. Koopman et. al. (reference 43 in the protocol) reviewed all these cited studies, along with several more, and still raised some of the same questions/concerns I have regarding the accuracy of various reported symptoms.
    a. This is especially true in the case of wheezing, which is the most commonly studied, yet probably most problematic, reported symptom.
        i. Members of non-wheezing families do not necessarily recognize a wheeze properly, and upper respiratory noises are difficult to differentiate from wheeze. "Whistling" is not much more helpful.
        ii. Even when families bring the child in to the office for possible "asthma" symptoms, it may not be as simple as it seems to help them precisely recognize/differentiate wheezing. It may take experience over time with variations on the theme, depending on how "classical" the child's presentation is, before they develop a more sensitive/specific ability.
        iii. Many languages do not have a precise (specific) equivalent for wheezing; and there can be interesting dialect/colloquial variants.
        iv. Many of our Spanish families report "ronco," which is almost as non-specific as "gripe." And not all are aware of other terms, such as "jadeo" or "chiflido."
        v. It is not clear that any of the reported surveys have been validated in different languages, Spanish or otherwise.
        vi. Trying to define/differentiate wheezing for the first time over the phone can be challenging and time-consuming, even for someone who knows the family/child.
    b. Even something as common, and seemingly simple, as a "cold" means different things to different people, and may include everything from a bout of allergic rhinitis to non-specific rhinorhea to a full-blown viral upper respiratory infection with fever, etc.
    c. Cough is less equivocal per se, but precisely characterizing its nature and frequency is more of a challenge. Moreover, though we all recognize "cough variant asthma," the prognostic value/significance of cough in infancy for later asthma is less clear.

d. Asking about a history of physician-diagnosed "asthma" may also over or under state the case, for several reasons:
    i. Physicians may variously apply the term asthma to one or more bouts of "reactive airway disease."
    ii. As Brooks et. al. (protocol reference #14) point out, "physicians may be more or less likely to attribute wheezing in a LBW child to 'asthma' depending on their belief that wheezing is expected in children born prematurely."
    iii. In the case of ELBW infants, outpatient physicians are more likely to carry on with a diagnosis of BPD or CLD of prematurity, rather than introduce the new term of "asthma" (or RAD), which can have other connotations to parents.
    iv. Without some further information concerning quality and quantity of symptoms, direction and magnitude of possible bias is hard to accurately assess.
e. Possible solutions would include one or more of the following:
    i. Some further definition/explanation of terms for families at the outset of the study, in oral and/or written form;
    ii. Some reminder/reinforcement during the phone interview, which would lengthen an already lengthy interview;
    iii. Some further validation through chart audit, which would be much more time consuming and much less feasible where primary care is not centralized.

2) Ascertainment of Outcomes
    a. For children who have had more than an isolated bout or two of one or more of the symptoms in the questionnaire, which necessitates answering another 4-9 questions for each leading positive symptom, the questionnaire can turn into a very long phone interview.
    b. Precision of recall of number of office visits, never mind dates of such, is going to be progressively limited, the greater the number of visits, even for periods as short as 6 months.
    c. Even for more dramatic events such as ER and hospitalization, precision of date recall is going to be limited.
    d. Koopman et. al. have suggested that recall bias may influence results.
    e. Though a centralized approach to phone interviews may have the benefits listed, it would not succeed with our families for the following reasons:
        i. A significant percentage of our families are not U.S. citizens, and would be very wary of anyone they have not met calling them, even if this was explained ahead of time.
        ii. Central staff do not have the same rapport or familiarity with the families that local study staff have.
        iii. Additional tracking/contacts by central staff would likely be more counterproductive than synergistic.

3) Additional Questionnaire Issues: Appendix B&C
    a. Questions 4a-j

   i. Question b., as a., may refer to more than one episode of wheezing, some of which may not have been associated with colds, whereas others were. (As noted above, "colds" is not defined.)
   ii. Question g. does not define "attacks"
b. Questions 6a-j
   i. Question b sounds as if it is referring to a single or "prototypical" episode, whereas both 6 (a) and b could well refer to multiple different types of episodes.
c. Questions 7a-f
   i. Questions e-f ask about the "past year" whereas the interval should only be 6 months for the 6, 12, and 18 month surveys.
d. Questions 8a-d
   i. Question a. appears to lump "any wheezing illness....not due to asthma" along with bronchiolitis. Not sure where BPD/CLD or bronchitis fit in to this equation.
e. Questions 11a-d
   i. Without knowing basis for diagnosis of pneumonia (exam +/- CXR +/- WBC), viral vs. bacterial, not sure what we can make of this history. Might at least want to ask about antibiotics and hospitalization.

From: Avroy A. Fanaroff
To: "Hastings Betty J."; Neil Finer
Cc: wrich@ucsd.edu; "Avroy A. Fanaroff M.D."; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"
Subject: RE: Pulse oximeter replacement on SUPPORT baby
Date: Thursday, May 26, 2005 6:39:17 PM

I would agree
Av
-------*Original Message*-------

From: Neil Finer
Date: 05/26/05 17:43:14
To: 'Hastings, Betty J.'
Cc: wrich@ucsd.edu; 'Avroy A. Fanaroff, M.D.'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'
Subject: RE: Pulse oximeter replacement on SUPPORT baby

Hi Betty

I would respond by saying that if the infant does not need oxygen for at least 8-12 hours per day that we should not use the study oximeters, and certainly not for a brief period around feedings..

Wade is traveling so I will copy him and see if he agrees

Any other thoughts?.

Neil

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Thursday, May 26, 2005 7:24 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu
Subject: FW: Pulse oximeter replacement on SUPPORT baby
Importance: High

Neil/Wade,

We need clarification regarding the question below. Thanks very much for your help.

Betty

-----Original Message-----
From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Thursday, May 26, 2005 10:07 AM
To: Hastings, Betty J.
Cc: Abbot Laptook
Subject: Pulse oximeter replacement on SUPPORT baby

Hi Betty,

Another question we need some clarification on:

If the pulse oximeter is d/ced prior to 36 wks GA but the baby subsequently requires oxygen for "feeds only" (prior to 36 wks) does this baby need to go back on the study pulse oximeter?

Thanks

Angelita

From: Hastings, Betty J.
To: Rebecca Bara
Cc: nxs5@cwru.edu; sshankar@med.wayne.edu; Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT oximeter
Date: Thursday, May 26, 2005 12:38:00 PM

Becky,
Thanks very much for letting me know. I will add this number to my tracking sheet.
Betty

-----Original Message-----
From: Rebecca Bara [mailto:ae5357@wayne.edu]
Sent: Thursday, May 26, 2005 12:34 PM
To: Hastings, Betty J.
Cc: nxs5@cwru.edu; sshankar@med.wayne.edu; higginsr@mail.nih.gov
Subject: SUPPORT oximeter

Hi Betty,

At Nancy Newman's request, we are shipping one of our SUPPORT study oximeters to Case Western by overnight delivery. The oximeter serial number is 313580 and the docking station serial number is 063721.

Thanks,
Becky

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT time in target range
Date: Wednesday, May 25, 2005 9:50:54 PM

Hi Rose
We probably could but do we want to do that much analysis at this stage?
I would wait till we see more data.
I'm not sure that we would see anything that would change what we are doing.
Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, May 25, 2005 10:45 AM
To: Duara, Shahnaz; nfiner@ucsd.edu; Wally Carlo, M.D.; edward.donovan@cchmc.org; Betty Hastings; Ken Poole; Michele; Wade Rich; Everett, Ruth; adas@rti.org
Subject: RE: SUPPORT time in target range

Can we separate out the room air babies from those that were actually in oxygen?
This could give us a better handle on what is going on.
Thanks
Rose

From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Tuesday, May 24, 2005 6:08 PM
To: nfiner@ucsd.edu; Wally Carlo, M.D.; edward.donovan@cchmc.org; Betty Hastings; Higgins, Rosemary (NIH/NICHD); Ken Poole; Michele; Wade Rich; Everett, Ruth; adas@rti.org
Subject: RE: SUPPORT time in target range

Hi all,

Sorry to sound like a stuck record, but this was exactly my fear when we decided to continue using the study POX once babies weaned to RA. This way we can't tell whether babies were appropriately handled (nothing to be done if in RA) or not. The other is a concern also, switching back and forth from study to standard POX by RA status, but in trying to reduce work for the RTs we may end up with high-end uninterpretable data.

Shahnaz

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, May 24, 2005 5:47 PM
To: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; Duara, Shahnaz; 'Wade Rich'
Subject: FW: SUPPORT time in target range

> Hi Everyone
> Here is the first data from the oximeters for your reading pleasure Its far too early to say much except that we are getting the data, and the time in the narrow target range is less than we would like. Remember however that some of the time these infants were in room air.
> Too my eyes, the biggest difference is the duration above 95%.
> Your thoughts??
> Be well

Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, May 24, 2005 2:03 PM
To: wrich@ucsd.edu; nfiner@ucsd.edu
Cc: Poole, W. Kenneth
Subject: SUPPORT time in target range

Neil and Wade,

Attached is a document showing the percent of time babies in the SUPPORT trial have been kept in the target SpO2 ranges. Separate percentages were calculated for the low and high SpO2 arms and for each center. Please note that these are the oximeter display values, not the actual SpO2 values. Also, note that the numbers are based on a very small number of babies. The tables include the number of babies and total number of hours of SpO2 data that went into calculating the percentages. The percent of time in each range is the overall percent of time babies at the center were kept in the range, as opposed to the average percent of time each baby was kept in the range. In other words, babies for whom more data were collected (over a longer period of time) are more heavily weighted in the percent calculations. If you have any questions regarding how these numbers were calculated, please let me know.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
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Research Triangle Park, NC 27709-2194
Telephone (919) 485-7780
Fax (919) 485-7762
mgantz@rti.org

From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Neil Finer
Subject: FW: growth prot1.doc
Date: Wednesday, May 25, 2005 5:19:08 PM
Attachments: growth prot1.doc

Hi Rose,

I have heard back from Rich, with his suggestions. He agrees that the protocol is worth doing as a SUPPORT secondary, and has made some good suggestions, particularly with respect to when we obtain snapshots of intake and anthropometric measurements. However, the main glitch is the budget. Any luck with co-funding for Susan's protocol?

Given an approximately 35% mortality in infants 24-27 weeks, we can limit the nutrition snapshots to just the survivors (est 858), which will save sig funds.
At 2 h/survivor that would still be $55K.

How do you suggest I proceed? I can have Cristina prepare the application for presentation as altered according to Brenda and Rich's input, with expanded data collection (and budget), discuss the different options for covering costs and go to vote, or limit ourselves to what we collect for GDB and miss an opportunity to fully explore this question.

I'm looking for some guidance here.
Thanks
Shahnaz

-----Original Message-----
From: Richard A. Ehrenkranz [mailto:richard.ehrenkranz@yale.edu]
Sent: Wednesday, May 25, 2005 3:09 PM
To: Duara, Shahnaz
Subject: Re: growth prot1.doc

Shahnaz:
I have reviewed this proposal. Overall I think that it is an appropriate
secondary study for the SUPPORT trial. I have some specific comments below: 1. Line 1 of abstract: I suggest you consider another phrase than

"postnatal growth retardation." Perhaps "postnatal growth restriction" or
"growth failure" or Poor postnatal growth".
2. Secondary hypothesis 1: Instead of "better" consider more rapid or greater. 3. Specific aim 3: Consider changing to "...at 36 wks PMA or discharge,
which ever comes first."
4. Specific aims 5-9: Can't these be combined into one specific aim that

relates growth to SpO2, with SpO2 expressed as a continuous variable of percentages of time infants were at different saturations?
5. Methods: [I agree with your "snapshot" idea, but I would choose

different ones.]
a. Anthropometric measures: I suggest: birth, postnatal day 7, day 14, day
21, and day 28; 32 wks PMA; 36 wks PMA or discharge (whichever is first). Delete 18-22 mos, as listed in follow-up data.
b. Clinical data: 24 hour intake: I suggest postnatal day 7, day 14, day

21, and day 28; 32 wks PMA; 36 wks PMA or discharge (whichever comes first). Delete 18-22 mos from 24 hour intake; I do not that information will be helpful.
6. Budget: I think that your estimate of 25 minutes is a too little. Probably more like 2-3 hours. Sorry, that makes your budget $84,480-$126,720.

I hope that this is helpful.
Richard

At 11:07 AM 5/18/2005 -0400, you wrote:
>Hi Richard,
>
>This is a copy of the Growth secondary that Cristina Navarette from our

>group is proposing for SUPPORT. As I told you at the PAS, the timing of

>the 'snap-shots' was based upon 'reasonable' for cross-sectional data,
>but we have nothing to tell us whether they pick up the overall intake
>trajectory or whether they can end up being misleading.
>
>Abhik and John Langer are mulling over the Glutamine data set to see
>whether it can be used for guidance, as I am. Any ideas would be very
>welcome.
>
>Shahnaz
> <<growth prot1.doc>>

Richard A. Ehrenkranz, MD
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Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study: A Proposed Secondary Study

Cristina Navarrete MD, and Shahnaz Duara MD
University of Miami Miller School of Medicine, Miami, FL.

Abstract:

Post-natal growth retardation is a major problem in preterm infants. Perturbations in oxygenation are recognized to influence post-natal growth; hypoxic conditions can directly impair growth and hyperoxic conditions predispose infants to BPD which in turn has been linked to poor growth. The NICHD Neonatal Network is conducting a prospective trial of preterm infants randomized to two levels of baseline oxygen saturations. The effect of baseline saturations on pulmonary morbidity and ROP are the primary outcome measures. With respect to post-natal growth, there is a paucity of data that relates alterations in baseline oxygen saturation and/or frequent deviations above or below the baseline to growth outcomes. We propose an ancillary study to quantify short-term growth velocity in-hospital and long-term growth at 18-22 months of corrected age for infants enrolled in the SUPPORT Trial in relationship to oxygen saturation.

A. Hypothesis to be tested

Primary:

1. Infants in the low oxygen saturation group (85-89%) will have better in-hospital and better long-term (18-22 months corrected age) growth.

Secondary:

1. Growth will be better in infants who spend > 50% of the time with daily median oxygen saturation between 85% -95% while on supplemental oxygen, independent of randomization to low or high oxygen saturation.

2. Infants with BPD will have poorer in-hospital and long-term growth than infants without BPD, independent of randomization to low or high oxygen saturation.

3. Long term growth will be positively related to neuro-developmental outcome, independent of randomization to low or high oxygen saturation.

B. Specific Aims:

1. To determine anthropometric measurements (wt, HC, length) in infants randomized to low and high oxygen saturation arms,

from birth to hospital discharge and again at 18-22 months corrected age.

2. To determine nutritional intake (parenteral and enteral) during hospital stay.
3. To determine the percentage of infants with growth <10 percentile at discharge.
4. To determine the percentage of infants with growth <10 percentile at 18-22 months corrected age.
5. To determine the proportion of time spent with oxygen saturation <85% and >95%, and relate to growth.
6. To determine the proportion of time spent with oxygen saturation 85-95%, and relate to growth
7. To determine the proportion of infants with median oxygen saturation 75% - 84%, and relate to growth.
8. To determine the proportion of infants with median oxygen saturation < 75%, and relate to growth.
9. To determine the proportion of infants with median oxygen saturation > 95%, and relate to growth.
10. To relate incidence of BPD in low and high saturation arms to growth.
11. To determine in-hospital growth velocity in low and high saturation arms.
12. To determine long-term growth velocity, from hospital discharge to follow up at 18-22 months corrected age in low and high saturation arms.
13. To relate neuro-developmental outcome at 18-22 months corrected age to long-term growth in low and high saturation arms.

Rationale:

The SUPPORT Trial will randomize infants to two ranges of SpO2 in order to test the hypothesis that use of a lower SpO2 range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity and/or the need for surgical intervention. Retrospective cohort data from several units in the U.K., with different oxygen supplementation policies, revealed poorer growth patterns in the preterm infants exposed to higher oxygen saturations for the duration of oxygen exposure (Tin 2001). Conversely, observational data of infants with established BPD show better growth with home oxygen support (Groothius 1987), and two recent RCT of different target saturations in older oxygen-dependent premature infants showed no difference in short or long-term growth outcomes (STOP-ROP 2000, BOOST Trial 2003). There are no RTC data evaluating the short or long-term growth impact of different SpO2 strategies with supplemental oxygen use in a birth cohort of extremely preterm infants. Therefore, this study provides an opportunity for us to obtain critically needed growth information on premature infants who are exposed from birth to different target oxygen saturation strategies.

Background

Improvements in antenatal care, respiratory support and nutrition have contributed to increased survival of ELBW infants. As the number of survivors increase, the long term outcome of these infants becomes more important. Lemons et al described growth failure or weight <10th percentile at 36 weeks postmenstrual age in 97% of ELBW infants surviving to discharge. Some morbidities in adulthood are linked to growth during the early post-natal period (Singhal 2004) and make adequacy of growth in this population of heightened interest.

Instead of following intra-uterine growth curves of age matched fetuses, VLBW infants exhibit wide-spread post-natal growth retardation (Cooke 2004), losing ground during the first weeks of life (Berry 1997). To resume growth post-natally, nutrition is of paramount importance; however, other factors such as severity of illness and perhaps oxygenation also play a role. Observational studies of infants with BPD showed poor post-natal growth when infants were sent home without oxygen supplementation (Markestad 1981).

Although preterm infants without lung disease attain oxygen saturations >95%, artificial attempts to keep arterial oxygenation at a "physiological" level may not be beneficial to growth, the lung or retina (Tin 2001). Animal studies have shown that newborn mammals (mice, rats, guinea pigs) develop poor growth with chronic hypoxia and that blunted body growth is directly proportional to the profundity of the exposure to chronic hypoxia (Mortola 1990). Chronic hypoxemia has also been suggested as the cause of poor growth in patients with cyanotic congenital heart disease (Dundar 2000). When home oxygen supplementation was discontinued inappropriately by parents in a cohort of VLBW infants with BPD, there was a deceleration in the rate of weight gain, which improved when oxygen supplementation was resumed (Groothius 1987). Hudak et al in 1989 observed that ELBW infants with CLD who went home on oxygen supplementation had good catch-up growth at 19 months. Taken collectively, these data suggest that hypoxic conditions affect growth negatively and supplementing oxygen may improve growth.

The optimal level of oxygen saturation to promote post-natal growth is unknown. Most of the available human data is limited to oxygen supplementation of infants who are oxygen dependent or have BPD. Baraldi et al demonstrated that discharged infants with BPD, who were kept on supplemental oxygen to keep saturations above 94%, had progressive but poor weight gain (stayed below 3rd percentile) at 9 months corrected age follow-up. In infants with BPD whose oxygen supplementation was intentionally discontinued, the subset who exhibited episodes of desaturations below 88-91% had a significant decline in the rate of weight gain as compared to those who maintained saturations above 92% (Moyer-Mileur 1996). Conversely, when two different oxygen saturation control policies (high: 88-98% and low: 70-90%) were retrospectively reviewed in <28 week gestation infants, the infants being cared for in the high oxygen saturation policy units were more likely to weigh less than the 3rd percentile at discharge

(45% vs. 17%, Tin 2001). The infants assigned to the high oxygen saturation limits were also more likely to have BPD and ROP.

Recently, the BOOST Trial demonstrated that randomizing infants born <30 weeks gestation who were still on oxygen at 32 weeks postmenstrual age either to standard saturations (91-94%) or to high saturations (95-98%) produced no significant difference in growth at 12 months corrected age. This study, while randomizing infants to two different levels of saturations (conventional and high), only enrolled infants if they were still on oxygen supplementation at 32 weeks PMA and used higher limits than planned by SUPPORT. Our proposal is novel in that randomization to the two oxygen strategies begins at birth and continues for as long as the infants are in supplemental oxygen - by implementing this secondary we will be able to determine the impact of these strategies on short and long-term growth.

Methods:

Collection of Data (some are already part of the GDB *)

Anthropometric Measures – at birth*, corrected age 28w (wt), 32w (wt), 36w*, status* and 18-22 months*

1. weight
2. length
3. head circumference

Clinical Data –

1. 24 h intake (Parenteral, Enteral) – at corrected age 28w, 32w, 36w, status and 18-22 months
2. Date of first enteral feed*
3. Date of full enteral feeds (enteral > 120ml/kg/d)*
4. Total number of days on parenteral nutrition*
5. Date when infant regained birth weight*
6. BPD Y/N (Physiological definition)*

Intervention Data –

1. Duration of time spent in target saturation ranges of interest (already part of SUPPORT‡)
2. Median values for unmasked oxygen saturation while still on supplemental oxygen therapy
3. Highest daily FiO2‡
4. Duration of supplemental oxygen exposure
5. Documentation of post-discharge oxygen use

Follow Up data

1. Anthropometric measurements at 18-22months corrected age
2. Neurodevelopmental follow up at 18-22 months corrected age

Primary Outcome:

Growth in-hospital and at 18-22 months corrected age in high and low saturation arms.

Sample Size:

Given the importance of using an RTC to establish the impact of different levels of oxygen saturation from birth on short and long term growth, recognizing the wealth of oxygen saturation data that will be available for analysis and the absence of comparable data in the literature, all infants in the SUPPORT Trial should be recruited into this secondary (n=1320)

Statistical Analysis:

Based upon intent-to-treat, differences between treatment arms of continuous data will be assessed by the Student t-test or the Mann-Whitney U-test, depending upon normal or skewed data distribution. Categorical data will be compared by chi-square. Linear regression will be used to determine the relationship between measures of oxygen saturation and growth. Logistic regression models will be developed to determine whether oxygen saturation independently affects growth after correction for confounding variables that also alter growth.

Discussion of Anticipated Results

We anticipate a better growth outcome in-hospital and at 18-22 months corrected age in the infants randomized to the lower target saturation range who maintained their median oxygen saturations within study range.

Budget

Time needed by research nurses to review subject records and collect additional anthropometric and nutritional data. Estimated time 25 minutes @ $32/h x 1320 patients =$17,600.00

References:

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From: Neil Finer
To: "Duara, Shahnaz"; "Wally Carlo, M.D."; edward.donovan@cchmc.org; "Betty Hastings"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Wade Rich"; "Everett, Ruth"; adas@rti.org
Subject: RE: SUPPORT time in target range
Date: Tuesday, May 24, 2005 7:44:31 PM

Hi Shahnaz
We debated this issue long and hard.
I'm not sure we should worry at present. Once we know the actual Fio2 ie RA or not this may become much less of an issue. We can link the download to the FiO2 for the study analyses, but not for this data as it is really for feedback.
We need much more data, and I am impressed that the 2 groups actually look grossly different for > 95%. This could be a very good thing for separation of the groups. Once we have 100-200, we'll turn Wally loose on the data.
Be well
Neil

From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Tuesday, May 24, 2005 3:08 PM
To: nfiner@ucsd.edu; Wally Carlo, M.D.; edward.donovan@cchmc.org; Betty Hastings; higginsr@mail.nih.gov; Ken Poole; Michele; Wade Rich; Everett, Ruth; adas@rti.org
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Shahnaz

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Sent: Tuesday, May 24, 2005 5:47 PM
To: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; Duara, Shahnaz; 'Wade Rich'
Subject: FW: SUPPORT time in target range

> Hi Everyone
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> Too my eyes, the biggest difference is the duration above 95%.
> Your thoughts??
> Be well
> Neil
>
> ---
>
> **From:** Gantz, Marie [mailto:mgantz@rti.org]
> **Sent:** Tuesday, May 24, 2005 2:03 PM
> **To:** wrich@ucsd.edu; nfiner@ucsd.edu
> **Cc:** Poole, W. Kenneth

Subject: SUPPORT time in target range

Neil and Wade,

Attached is a document showing the percent of time babies in the SUPPORT trial have been kept in the target SpO2 ranges. Separate percentages were calculated for the low and high SpO2 arms and for each center. Please note that these are the oximeter display values, not the actual SpO2 values. Also, note that the numbers are based on a very small number of babies. The tables include the number of babies and total number of hours of SpO2 data that went into calculating the percentages. The percent of time in each range is the overall percent of time babies at the center were kept in the range, as opposed to the average percent of time each baby was kept in the range. In other words, babies for whom more data were collected (over a longer period of time) are more heavily weighted in the percent calculations. If you have any questions regarding how these numbers were calculated, please let me know.

Marie

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From:	Neil Finer
To:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"
Subject:	FW: SUPPORT time in target range
Date:	Tuesday, May 24, 2005 5:46:46 PM
Attachments:	Oximeter display values 5-24-05.rtf

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PERCENT OF TIME SPENT IN EACH RANGE (OXIMETER DISPLAY)

LOW TREATMENT GROUP: PERCENT OF TIME SPENT IN EACH RANGE (OXIMETER DISPLAY)

Center Number	Number of babies	Total number of hours	<85	>=85 and <88	TARGET >=88 and <=92	>92 and <=95	>95
11	1	501.1	8.3	1.6	14.7	18.8	56.6
12	1	378.9	14.7	9.0	44.3	8.7	23.3
14	4	2059.4	10.8	2.4	19.1	19.9	47.8
16	1	999.5	8.4	1.7	13.8	18.3	57.7
18	1	162.7	0.6	0.0	0.4	0.8	98.1
22	5	2207.0	12.6	2.1	14.2	16.7	54.3

HIGH TREATMENT GROUP: PERCENT OF TIME SPENT IN EACH RANGE (OXIMETER DISPLAY)

Center Number	Number of babies	Total number of hours	<85	>=85 and <88	TARGET >=88 and <=92	>92 and <=95	>95
12	2	1445.9	15.4	9.1	35.6	20.4	19.5
14	3	2545.4	15.0	9.0	44.2	8.2	23.6
16	1	772.3	14.6	8.5	48.9	7.6	20.5
18	1	200.9	1.7	3.7	60.0	15.1	19.4
22	1	682.9	4.6	3.3	21.2	8.1	62.8

From: Higgins, Rosemary (NIH/NICHD)
To: Charles Rosenfeld
Subject: RE: UT Southwestern Authorship
Date: Monday, May 23, 2005 4:20:00 PM

Charles
It is fine to designate Walid at the PI for the aEEG and SUPPORT Trials. This issue sometimes comes up at the beginning of trials, but more often as the manuscripts get circulated. Will he also be the Dallas investigator for Candida? Is he writing (or co-authoring) any of the papers from the Benchmarking trial?
Other PI's have done this - the two most recent examples are Mike Cotten from Duke and Ronnie Guillet from Rochester as the PIs on the hypothermia manuscript in Lieu of Ron Goldberg and Dale Phelps. This is done at the discretion of the site PI, so it is fine for you to designate Walid as the author for papers.

Thanks
Rose

-----Original Message-----
From: Charles Rosenfeld [mailto:Charles.Rosenfeld@UTSouthwestern.edu]
Sent: Monday, May 23, 2005 4:00 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: UT Southwestern Authorship

Rose:

Sorry I did not see and speak with you at the meeting in DC. It was hectic to say the least and I tried to spend time with my son whoc work for USAID and their food distribution program. By the way, your presentation was good.

In looking at what recognition might be be given to our site in abstracts and/or papers, I would like for you to use Walid Salhab as the person to cite. He has ushered the protocols through the IRB with revisions, superivsed the research nurses, and in-serviced the staff for every study in the past 2 years. The failure or success of the aEEG study and now the SUPPORT are definitely due to him. He has put in the time and needs the recognition for his work. As you are aware, I do not need that.

Please let me know your thoughts. We are preparing a letter re our wish to continue in the Network, but Pablo Sanchez is likely to be the PI.

Charles

Charles R. Rosenfeld, M.D.
George L. MacGregor Professor of Pediatrics
and Professor of Obstetrics and Gynecology
Director, Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd.
Dallas, TX 75390-9063
Telephone: (214) 648-3903
FAX: (214) 648-2481
Email: charles.rosenfeld@utsouthwestern.edu

From:	Neil Finer
To:	Giacoia, George (NIH/NICHD) [E]
Cc:	"Kattwinkel, John *HS"; rxm6@po.cwru.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject:	RE:
Date:	Monday, May 23, 2005 1:32:36 PM
Attachments:	Apnea of Prematurity- Workshop - FinalRevised May 23 05.doc

Congratulations George
Rose, please look at this and ensure that this is the final version, I think the final version came from you. I have only split the Table.
I have broken the Table into 2. Please have a quick look. I will let the editors decide how to best space.
Thanks and Regards
Neil Finer

From: Giacoia, George (NIH/NICHD) [mailto:giacoiag@exchange.nih.gov]
Sent: Sunday, May 22, 2005 10:29 AM
To: 'nfiner@ucsd.edu'
Cc: Mattison, Donald (NICHD)
Subject:

Dear Neill:
I am pleased to tell you that the articles for the Supplement in Pediatrics have been accepted with minor editorial changes (see attached file)
One of the reviewers has asked that you consider the following changes :

Table I although extensive is quite unwieldy... Is it possible to separate into 2 tables? in the Future Research Needs section, the last two statements on p.157 are very general. examples should be provided.

Please send me within a week the changes and/or rebuttal to the reviewers suggestions . At this time do not go to the Pediatric Web page.
I need to compose an overall response for Dr. Feigin that responds to all three reviewers ' concerns
If you have questions please call me
George

Apnea of Prematurity

Presented by Rosemary Higgins, M.D., John Kattwinkel, M.D., and Richard J. Martin, M.D.

Background

Apnea of prematurity (AOP) is the most common and frequently recurring problem in VLBW infants. AOP is found in more than 50 percent of premature babies and is almost universal in babies smaller than 1,000 grams. The literature defines clinically significant apnea in infants as breathing pauses lasting more than 20 seconds, or more than 10 seconds if associated with bradycardia (e.g., less than 80 beats per minute) or oxygen desaturation (e.g., O_2 saturation of less than 80 to 85 percent). This definition may vary depending on geographic location or the baby's symptomatology. Moreover, there is no consensus about the duration of apnea that is considered pathological, and there is no agreement regarding the degree of change in oxygen saturation or severity of bradycardia that constitutes a true apnea event.

Although scientists cannot yet say whether AOP causes a clinically certain outcome and is harmful, providing no treatment when a baby stops breathing in the NICU is not an option. The immediate and irresistible urge to respond to apnea is based partly on the uncertainty about exactly what causes the apneic episode and whether the unknown causative factor might also harm the brain or other systems and produce a long-term effect on neurodevelopment. Although caregivers are able to respond successfully to apnea events with drugs (as well as physical and mechanical interventions) in the NICU, it remains unproven whether such interventions have any other long-term effects, good or bad. One of the most effective drugs, caffeine citrate, is currently labeled for short-term use only, within a limited gestational age population. Moreover, most premature babies also suffer from gastroesophageal reflux disease (GERD), and many clinicians use off-label drugs approved for GERD in the belief that such treatments also have an impact on AOP, although this link has never been demonstrated.

Treatment Issues

Before the workshop, the Pulmonary Work Group identified the following key issues concerning the treatment of AOP:

- The definition, diagnosis and treatment of the condition have not been standardized.
- The benefit of intervention, apart from a reduction in apnea itself, remains largely unproven.
- Most studies of apnea have not collected real-time data documenting the actual event and the preceding baseline, including physiologic parameters such as oxygen saturation.

- Few studies have evaluated sustained treatment improvement at 7 days or later after the initiation of therapy, and the improvements noted at 1 to 3 days after therapy usually are not sustained at 1 week.

- Most studies are small in number and thus are not stratified by birth weight, gestation, postconceptional age, or disease or disease processes that have occurred in individual babies.

- Previous studies have not addressed confounding conditions such as hypoxemia, the requirement for oxygen therapy, pharmacologic sedation, glucocorticoid therapy, acute or chronic lung disease, PDA, IVH, sepsis, or other treatments such as dopamine.

- No good evidence exists to support the view that apnea and reflux are temporarily or causally related and that the use of antireflux medications (e.g., cisapride, metaclopramide) decreases apneas.

- The most important issue is the role of apnea in determining infants' long-term neurodevelopmental outcomes.

Study Design Issues

The Pulmonary Work Group summarized study design issues that it identified in four basic categories.

Important Questions About Neonatal Apnea

The work group agreed that the following key questions need to be addressed as a priority:

- Does neonatal apnea affect long-term neurodevelopmental outcome, or is it merely a marker of other complications of prematurity?

- Is xanthine, the primary drug currently used to treat apnea, and other future drug therapy for AOP associated with improved outcome, both short-term and long-term?

- Does esophageal reflux cause apnea, and, if so, are pharmacologic therapies effective, both for the reflux and the apnea?

Other secondary questions about apnea include the following:

- What is the effect of xanthines on GERD (e.g., potentiation)?

- What is the most effective way to intervene for apnea (i.e., pharmacologic versus mechanical intervention)?

- Does the etiology of apnea affect response to therapy?
- What are the response and the associated risk as a function of GA and weight?
- What is the appropriate threshold for treatment?
- Is xanthine use outside the hospital setting for postneonatal infants safe and effective?
- Are other agents (e.g., other adenosine inhibitors, progestins) effective and safe in treating AOP?
- What is the effect of baseline oxygenation on the incidence and severity of apnea?
- Are there legitimate uses of xanthines for apnea disorders other than AOP (e.g., to counteract apnea associated with prostaglandin administration, for apparent life-threatening event, for post-anesthesia apnea)?
- What is the relationship of body and head position to apnea?
- What is the appropriate dosing regimen for pharmacologic agents commonly used to treat AOP (e.g., caffeine, doxapram)? What are the toxicities or side effects?
- Is prophylactic use of xanthines for AOP safe and effective?

Methodology Requirements for Study

The Pulmonary Work Group identified the following important methodological requirements for studies:

- Studies should include simultaneous assessment of multiple relevant variables, with minimal inclusions being chest wall movement, heart rate, and oximetry.
- A portion of the study population or study time should include an assessment of nasal airflow to distinguish between central and obstructive apnea.
- AOP must be uniformly defined (e.g., apnea duration of 20 seconds, or 10 to 20 seconds if accompanied by bradycardia [< 80 beats per minute] or desaturation [SpO2 < 80%]). The work group was unable to resolve a concern about failing to account for apnea events of less than 10 seconds' duration that are associated with significant bradycardia/desaturation.
- Studies should examine treatment duration over the long term (e.g., several weeks) and over a wider range of GAs. The work group noted that current caffeine labeling is for short-term use and 28 to 32 weeks GA.

- Studies must control for conditions believed both to cause apnea and to independently influence outcome (e.g., IVH, PVL, respiratory distress syndrome, BPD, reflux).

- Studies must be randomized and blinded.

- It is appropriate to conduct studies examining reflux treatment and its effect on apnea without necessarily including measurement of reflux. The work group acknowledged that no good evidence is available to support the relationship; nevertheless, clinicians continue to use it. Although apnea and GERD occur in nearly all premature babies, they may be unrelated. The work group agreed that it was important to bridge the investigation of this issue between the gastrointestinal community and neonatologists because both groups are examining it independently.

Appropriate Outcome Measures

The Pulmonary Work Group agreed that studies need to include and be powered for short-term, intermediate-term, and long-term outcomes. (See proposed clinical trial framework below for more details.)

Ethical Considerations for Future Studies

The Pulmonary Work Group made the following determinations about ethical considerations:

It is ethical to perform randomized placebo-controlled trials for apnea in preterm infants. The work group recognized that placebo does not mean there is no treatment for apnea. The availability of other treatments such as CPAP and mechanical ventilation makes a placebo-controlled trial ethicalIt is ethical to perform randomized placebo-controlled trials for reflux (not involving apnea) in preterm infants.

- It is ethical to perform randomized placebo-controlled trials for reflux and apnea, with apnea being the outcome, in preterm infants.

Proposed Clinical Trial Framework

The Pulmonary Work Group proposed a sample framework for the study of apnea in neonates. The design included the characteristics listed in the text box below.

FRAMEWORK FOR STUDIES OF APNEA IN NEONATES
HYPOTHESES, OUTCOMES, AND STRATIFICATION

- **Hypothesis**—There is no difference in outcome between patients managed with drug X for apnea versus placebo. Subhypotheses would include the following:
  - There is no difference in apnea (frequency and severity) at predetermined times sequentially measured between drug X and placebo.
  - There is no correlation between apnea (frequency and severity) and neurodevelopmental outcome.
- **Drug priorities**—The following drugs should be used in studies of apnea (in order of priority):
  - Caffeine (Dose-ranging studies with development will need to be performed.)
  - GERD agents for treatment of apnea
  - Drugs for future consideration include specific adenosine receptor subtype antagonists, doxapram, and progesterone
- **Primary Outcome**—The study should be powered for neurodevelopmental outcome at 18 months.
- **Secondary outcomes**—Proposed secondary outcomes include the following:
  - Length of hospitalization
  - Number of days hospitalized for apnea only
  - Frequency and severity of apnea events (measured 2 days after initiation of therapy and weekly until discharge)
  - Duration of assisted ventilation/continuous positive airway pressure (CPAP)
- **Type of study**—The study should be a randomized, blinded, multicenter, placebo-controlled trial.
- **Stratification**—Neonatal groups would be stratified by the following criteria:
  - < 800 grams
  - 800 to 1,200 grams
  - 1,200 to 1,500 grams

FRAMEWORK FOR STUDIES OF APNEA IN NEONATES
SAMPLE SIZE, CRITERIA, AND MEASURED PARAMETERS

- **Sample size**—The work group proposed a range of sample sizes based on a first-pass power analysis, given neurodevelopmental outcome versus control (80 percent power):
  - 3,000 patients to discern a 5-percent difference in incidence of some disorder, (e.g., 30 percent vs. 25 percent)
  - 500 patients to discern a 5-point difference in the Bayley score (SD15)
- **Entry criteria**—Entry criteria would require consideration of the following issues:
  - Use of periextubation caffeine
  - Use of prophylaxis, particularly for very immature infants
  - Use of a nonprophylaxis strategy that might require defining frequency and duration
- **Exclusion criteria**—Infants with the following characteristics would be excluded from the study:
  - Apnea judged to be primarily caused by an alternative etiology (not AOP; e.g., IVH, sepsis)
  - Congenital anomalies
  - Prior study drug exposure
- **Assessment parameters**—The work group identified the following assessment parameters for efficacy, safety, and PK:
  - Short-term parameters include the following:
    - Frequency, severity, and duration of apnea episodes at periodic time points throughout hospitalization with direct measures of actual apnea and the associated heart rate and SpO2
    - PK information for various GAs and CAs
  - Intermediate parameters include the following:
    - Various assessments of duration (e.g., duration of hospitalization, assisted ventilation [both CPAP and IPPV], O2)
    - Morbidities (NEC, IVH, PVL, BPD, ROP)
  - Long-term parameters include cognitive and psychomotor assessment.

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Future Research Needs

The Pulmonary Work Group identified the following future research needs:

- A large prospective study is needed to distinguish the role of apnea from the many confounding conditions and other predictors of neurodevelopmental outcome, including GA, neuroanatomic abnormalities, exposure to mechanical ventilation, sepsis, and occurrence of BPD.

- Studies and their analyses should include rigorous control of potentially confounding variables.

- Randomized trials ideally should have a primary hypothesis or co-primary hypotheses powered to assess long-term followup.

Plenary Discussion

During the plenary session, Pulmonary Work Group members and other workshop participants made the following points about the study of apnea in neonates:

- The issue of confounding therapies and morbidities when examining long-term outcomes is an important one that will need to be addressed, perhaps with statistical techniques. The work group considered excluding the smallest babies, who were likely to have comorbidities, but group members believed that the smallest babies were the ones most in need of intervention for apnea and were receiving prophylactic therapy. Multiple variables should fall out if the RCT is large enough.

- Although maturation is more relevant than size to respiratory drive, the work group chose to categorize infants by birth weight because it is more precise than GA.

- The work group may need to consult available PK data to the address the issue of whether to adjust drug doses to maintain the same serum levels as the baby grows.

- Many monitoring systems that record retrievable data on heart rate, respiratory rate, and oxygen saturation offer opportunities for documenting apnea events. Nurse observations clearly have been shown to be unreliable in documenting apnea episodes.

- The work group's proposed study is exploring questions that are different from the xanthine study being conducted by Dr. Barbara Schmidt's research group, which is not specifically addressing apnea. Although the work group's study would build on any results from Dr. Schmidt's study, it would explore new territory by asking whether an association exists between AOP and impaired neurodevelopmental outcome and, if so, whether the association is causal. Answering the second question would require an intervention to reduce apnea.

- The work group did not discuss the issue of the potential confounding effect of xanthine, which might affect growth and, thus, long-term outcome. A suggested approach to addressing the issue was to record birth rate velocity.

- The framework will address differentiation between central and obstructive apnea by having a subset of the study measure nasal airflow. This assessment would not be conducted for the entire study because it is impractical to measure airflow on a continuing basis.

- The work group considered the issue of nonapnea desaturation and was unable to resolve concerns about defining AOP in a way that would miss apnea events of less than 10-second duration. The final design of the study will need to address whether to include all events, including two to three second apneas.

From: Duara, Shahnaz
To: adas@rti.org
Cc: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Date: Sunday, May 15, 2005 11:10:46 PM
Attachments: growth prot1.doc

Hi Abhik,

I am forwarding you a protocol that we have suggested as a SUPPORT secondary. Most of the sub-committee met at dinner this evening in DC and the big question going around revolved around the collection of nutrition data. In an effort to reduce labor/cost while yet getting a measure of a variable (nutritional intake) that may be unbalanced between groups and independently affect growth, we introduced the idea of nutrition snap-shots at corrected ages 28 w, 32 w, 36 w, status and 18-22 months of age. For a secondary, we felt this was reasonable additional data collection.

Neil asked Brenda Poindexter to review the protocol - her major comment was that snap-shots would not be accurate and that we should instead collect daily nutrition data as was done in the glutamine trial. Our question for you, to pass on to John Langer, is the following - has the nutrition data from glutamine been queried in a way that would help us decide whether the snap-shots in time we selected will prove to be accurate in approximating intake? Are there better time points that we could think of substituting? Any additional information based on fact would be very helpful.

Thanks
Shahnaz

Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study: A Proposed Secondary Study

Cristina Navarrete MD, and Shahnaz Duara MD
University of Miami Miller School of Medicine, Miami, FL.

Abstract:

Post-natal growth retardation is a major problem in preterm infants. Perturbations in oxygenation are recognized to influence post-natal growth; hypoxic conditions can directly impair growth and hyperoxic conditions predispose infants to BPD which in turn has been linked to poor growth. The NICHD Neonatal Network is conducting a prospective trial of preterm infants randomized to two levels of baseline oxygen saturations. The effect of baseline saturations on pulmonary morbidity and ROP are the primary outcome measures. With respect to post-natal growth, there is a paucity of data that relates alterations in baseline oxygen saturation and/or frequent deviations above or below the baseline to growth outcomes. We propose an ancillary study to quantify short-term growth velocity in-hospital and long-term growth at 18-22 months of corrected age for infants enrolled in the SUPPORT Trial in relationship to oxygen saturation.

A. Hypothesis to be tested

Primary:

1. Infants in the low oxygen saturation group (85-89%) will have better in-hospital and better long-term (18-22 months corrected age) growth.

Secondary:

1. Growth will be better in infants who spend > 50% of the time with daily median oxygen saturation between 85% -95% while on supplemental oxygen, independent of randomization to low or high oxygen saturation.

2. Infants with BPD will have poorer in-hospital and long-term growth than infants without BPD, independent of randomization to low or high oxygen saturation.

3. Long term growth will be positively related to neuro-developmental outcome, independent of randomization to low or high oxygen saturation.

B. Specific Aims:

1. To determine anthropometric measurements (wt, HC, length) in infants randomized to low and high oxygen saturation arms,

from birth to hospital discharge and again at 18-22 months corrected age.

2. To determine nutritional intake (parenteral and enteral) during hospital stay.
3. To determine the percentage of infants with growth <10 percentile at discharge.
4. To determine the percentage of infants with growth <10 percentile at 18-22 months corrected age.
5. To determine the proportion of time spent with oxygen saturation <85% and >95%, and relate to growth.
6. To determine the proportion of time spent with oxygen saturation 85-95%, and relate to growth
7. To determine the proportion of infants with median oxygen saturation 75% - 84%, and relate to growth.
8. To determine the proportion of infants with median oxygen saturation < 75%, and relate to growth.
9. To determine the proportion of infants with median oxygen saturation > 95%, and relate to growth.
10. To relate incidence of BPD in low and high saturation arms to growth.
11. To determine in-hospital growth velocity in low and high saturation arms.
12. To determine long-term growth velocity, from hospital discharge to follow up at 18-22 months corrected age in low and high saturation arms.
13. To relate neuro-developmental outcome at 18-22 months corrected age to long-term growth in low and high saturation arms.

Rationale:

The SUPPORT Trial will randomize infants to two ranges of SpO2 in order to test the hypothesis that use of a lower SpO2 range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity and/or the need for surgical intervention. Retrospective cohort data from several units in the U.K., with different oxygen supplementation policies, revealed poorer growth patterns in the preterm infants exposed to higher oxygen saturations for the duration of oxygen exposure (Tin 2001). Conversely, observational data of infants with established BPD show better growth with home oxygen support (Groothius 1987), and two recent RCT of different target saturations in older oxygen-dependent premature infants showed no difference in short or long-term growth outcomes (STOP-ROP 2000, BOOST Trial 2003). There are no RTC data evaluating the short or long-term growth impact of different SpO2 strategies with supplemental oxygen use in a birth cohort of extremely preterm infants. Therefore, this study provides an opportunity for us to obtain critically needed growth information on premature infants who are exposed from birth to different target oxygen saturation strategies.

Background

Improvements in antenatal care, respiratory support and nutrition have contributed to increased survival of ELBW infants. As the number of survivors increase, the long term outcome of these infants becomes more important. Lemons et al described growth failure or weight <10th percentile at 36 weeks postmenstrual age in 97% of ELBW infants surviving to discharge. Some morbidities in adulthood are linked to growth during the early post-natal period (Singhal 2004) and make adequacy of growth in this population of heightened interest.

Instead of following intra-uterine growth curves of age matched fetuses, VLBW infants exhibit wide-spread post-natal growth retardation (Cooke 2004), losing ground during the first weeks of life (Berry 1997). To resume growth post-natally, nutrition is of paramount importance; however, other factors such as severity of illness and perhaps oxygenation also play a role. Observational studies of infants with BPD showed poor post-natal growth when infants were sent home without oxygen supplementation (Markestad 1981).

Although preterm infants without lung disease attain oxygen saturations >95%, artificial attempts to keep arterial oxygenation at a "physiological" level may not be beneficial to growth, the lung or retina (Tin 2001). Animal studies have shown that newborn mammals (mice, rats, guinea pigs) develop poor growth with chronic hypoxia and that blunted body growth is directly proportional to the profundity of the exposure to chronic hypoxia (Mortola 1990). Chronic hypoxemia has also been suggested as the cause of poor growth in patients with cyanotic congenital heart disease (Dundar 2000). When home oxygen supplementation was discontinued inappropriately by parents in a cohort of VLBW infants with BPD, there was a deceleration in the rate of weight gain, which improved when oxygen supplementation was resumed (Groothius 1987). Hudak et al in 1989 observed that ELBW infants with CLD who went home on oxygen supplementation had good catch-up growth at 19 months. Taken collectively, these data suggest that hypoxic conditions affect growth negatively and supplementing oxygen may improve growth.

The optimal level of oxygen saturation to promote post-natal growth is unknown. Most of the available human data is limited to oxygen supplementation of infants who are oxygen dependent or have BPD. Baraldi et al demonstrated that discharged infants with BPD, who were kept on supplemental oxygen to keep saturations above 94%, had progressive but poor weight gain (stayed below 3rd percentile) at 9 months corrected age follow-up. In infants with BPD whose oxygen supplementation was intentionally discontinued, the subset who exhibited episodes of desaturations below 88-91% had a significant decline in the rate of weight gain as compared to those who maintained saturations above 92% (Moyer-Mileur 1996). Conversely, when two different oxygen saturation control policies (high: 88-98% and low: 70-90%) were retrospectively reviewed in <28 week gestation infants, the infants being cared for in the high oxygen saturation policy units were more likely to weigh less than the 3rd percentile at discharge

(45% vs. 17%, Tin 2001). The infants assigned to the high oxygen saturation limits were also more likely to have BPD and ROP.

Recently, the BOOST Trial demonstrated that randomizing infants born <30 weeks gestation who were still on oxygen at 32 weeks postmenstrual age either to standard saturations (91-94%) or to high saturations (95-98%) produced no significant difference in growth at 12 months corrected age. This study, while randomizing infants to two different levels of saturations (conventional and high), only enrolled infants if they were still on oxygen supplementation at 32 weeks PMA and used higher limits than planned by SUPPORT. Our proposal is novel in that randomization to the two oxygen strategies begins at birth and continues for as long as the infants are in supplemental oxygen - by implementing this secondary we will be able to determine the impact of these strategies on short and long-term growth.

Methods:

Collection of Data (some are already part of the GDB *)

Anthropometric Measures – at birth*, corrected age 28w (wt), 32w (wt), 36w*, status* and 18-22 months*

1. weight
2. length
3. head circumference

Clinical Data –

1. 24 h intake (Parenteral, Enteral) – at corrected age 28w, 32w, 36w, status and 18-22 months
2. Date of first enteral feed*
3. Date of full enteral feeds (enteral > 120ml/kg/d)*
4. Total number of days on parenteral nutrition*
5. Date when infant regained birth weight*
6. BPD Y/N (Physiological definition)*

Intervention Data –

1. Duration of time spent in target saturation ranges of interest (already part of SUPPORT‡)
2. Median values for unmasked oxygen saturation while still on supplemental oxygen therapy
3. Highest daily FiO2‡
4. Duration of supplemental oxygen exposure
5. Documentation of post-discharge oxygen use

Follow Up data

1. Anthropometric measurements at 18-22months corrected age
2. Neurodevelopmental follow up at 18-22 months corrected age

Primary Outcome:

Growth in-hospital and at 18-22 months corrected age in high and low saturation arms.

Sample Size:

Given the importance of using an RTC to establish the impact of different levels of oxygen saturation from birth on short and long term growth, recognizing the wealth of oxygen saturation data that will be available for analysis and the absence of comparable data in the literature, all infants in the SUPPORT Trial should be recruited into this secondary (n=1320)

Statistical Analysis:

Based upon intent-to-treat, differences between treatment arms of continuous data will be assessed by the Student t-test or the Mann-Whitney U-test, depending upon normal or skewed data distribution. Categorical data will be compared by chi-square. Linear regression will be used to determine the relationship between measures of oxygen saturation and growth. Logistic regression models will be developed to determine whether oxygen saturation independently affects growth after correction for confounding variables that also alter growth.

Discussion of Anticipated Results

We anticipate a better growth outcome in-hospital and at 18-22 months corrected age in the infants randomized to the lower target saturation range who maintained their median oxygen saturations within study range.

Budget

Time needed by research nurses to review subject records and collect additional anthropometric and nutritional data. Estimated time 25 minutes @ $32/h x 1320 patients =$17,600.00

References:

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Askie LM, Henderon-Smart DJ. Cochrane Review "Restricted versus liberal exposure for preventing morbidity and mortality in preterm or low birth weight infants", last updated October 2003.

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Cooke RJ, Ainsworth SB, Fenton AC. Postnatal growth retardation: a universal problem in preterm infants. Arch Dis Child Fetal Neonatal Ed 2004; 89: F428-F430

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Groothius JR, Rosenberg AA. Home oxygen promotes weight gain in infants with BPD. Am J Dis Child 1987; 141: 992-5

Hudak BB, Allen MC, Hudak ML, Loughlin GM. Home oxygen therapy for CLD in ELBW infants. AJDC 1989; 143: 357-360

Lemons JA, Bauer CR, et al for NICHD Neonatal Research Network. Very low birth weight outcomes of the National Institute of Child Health and Development Neonatal Research Network, January 1995 through December 1996. Pediatrics 2001; 107(1)

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The STOP-ROP Multicenter Study Group. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics 2000; 105:295-310

Tin W, Milligan DWA, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001; 84: F106-110

From: Mcdavid, Georgia E
To: betty" <; Poole, W. Kenneth; petrie@rti.org; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Morris, Brenda H
Subject: Support death
Date: Friday, May 13, 2005 4:24:49 PM

Infant GDB# (b) (6) DOB (b) (6) expired (b) (6) was enrolled in the SUPPORT trial and randomized to CPAP in the DR. The infant did make it out of the delivery room on CPAP but was intubated within a few hours. It is unlikely that the death had anything to do with the study. SAE to follow.

From: Higgins, Rosemary (NIH/NICHD)
To: Mcdavid, Georgia E
Subject: RE: support death
Date: Thursday, May 12, 2005 2:54:00 PM

Thanks

From: Mcdavid, Georgia E [mailto:Georgia.E.McDavid@uth.tmc.edu]
Sent: Thursday, May 12, 2005 2:53 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: support death

Rose,
No, this infant was intubated for resuscitation purposes in the delivery room. There was never any attempt at CPAP.
Georgia

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 12, 2005 10:00 AM
To: Mcdavid, Georgia E
Subject: RE: support death

Georgia
Did you think the death was study related?
Thanks
Rose

From: Mcdavid, Georgia E [mailto:Georgia.E.McDavid@uth.tmc.edu]
Sent: Thursday, May 12, 2005 11:47 AM
To: betty" <; Poole, W. Kenneth; petrie@rti.org; Higgins, Rosemary (NIH/NICHD)
Cc: Morris, Brenda H
Subject: support death

Infant GDB# (b) (6) DOB (b) (6) expired at < 12 hours of age. The infant was randomized to CPAP in the DR but required intubation, epi, and chest compressions. COD was extreme prematurity. SAE to follow.

From: Duara, Shahnaz
To: nfiner@ucsd.edu; wcarlo@peds.uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: New SUPPORT Form
Date: Wednesday, May 11, 2005 4:33:05 PM

Hi Neil and Wally,

Ruth had a question regrading the 24 hour dump vis-a-vis the pilot. Are you OK with Wade's suggestion that she do the dump at the end of te week and let Scott separate out Day 1 info?

Shahnaz
-----Original Message-----
From: Everett, Ruth [mailto:REverett@med.miami.edu]
Sent: Wednesday, May 11, 2005 3:46 PM
To: Duara, Shahnaz
Subject: FW: New SUPPORT Form

Here is the original e-mail I sent Wade.

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, May 11, 2005 8:55 AM
To: Everett, Ruth
Subject: RE: New SUPPORT Form

Violations I can live with. The SAEs on the other hand...

From: Everett, Ruth [mailto:REverett@med.miami.edu]
Sent: Wednesday, May 11, 2005 6:48 AM
To: wrich@ucsd.edu
Subject: RE: New SUPPORT Form

So far so good! Lets just see how the 14 days go by without any violations.

> -----Original Message-----
> **From:** Wade Rich [mailto:wrich@ucsd.edu]
> **Sent:** Wednesday, May 11, 2005 8:46 AM
> **To:** Everett, Ruth
> **Cc:** nfiner@ucsd.edu
> **Subject:** RE: New SUPPORT Form
>
> Ruth,
> I am not at all clear about the pilot plan. Scott can always pull of that 24 hours, but if it were me I would save that data to a file, not erase your data, and then just continue until your regular download day. Congrats on your enrollment ! Did everything go OK?
> Wade
>
> ---
>
> **From:** Everett, Ruth [mailto:REverett@med.miami.edu]
> **Sent:** Wednesday, May 11, 2005 6:37 AM
> **To:** wrich@ucsd.edu
> **Subject:** RE: New SUPPORT Form
>
> Hello Wade, how did you read my mind? I was just thinking about you because we are up and

running, and have enrolled 1 baby, consented 3 and one refused. So what I wanted to know is regarding the down load, because I am part of the oxygenation pilot should I down load day one and send it to Scott, or just hold off and down load this baby once a month or every two weeks. However initially I think I am going to down load every week. When you get a chance let me know what you think.

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Tuesday, May 10, 2005 4:38 PM
To: ahensman@wihri.org; mbball@leland.stanford.edu; grisbyca@email.uc.edu; ellen_hale@oz.ped.emory.edu; gaynelle.hensley@utsouthwestern.edu; 'Mcdavid, Georgia E'; auten002@mc.duke.edu; linda_reubens@urmc.rochester.edu; lucmille@iupui.edu; mcollins@peds.uab.edu; Nancy.Miller@utsouthwestern.edu; 'Nancy Newman'; npeters@wfubmc.edu; monica.konstantino@yale.edu; ae5357@wayne.edu; rbridge@ucsd.edu; risa.demetrio@sharp.com; kathy.arnell@sharp.com; Everett, Ruth; brenda.H.Morris@uth.tmc.edu; cotte010@mc.duke.edu; crosen@mednet.swmed.edu; vanmeurs@leland.stanford.edu; kurt.schibler@cchmc.org; alaptook@wihri.org; Jobea0@chmcc.org; bpoindex@iupui.edu; edward.donovan@chmcc.org; jlemons@iupui.edu; moshea@wfubmc.edu; sshankar@med.wayne.edu; Duara, Shahnaz; susie.buchter@oz.ped.emory.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; Vineet.bhandari@yale.edu; vivek.Narendran@cchmc.org; Walid.Salhab@utsouthwestern.edu; (b) (6) 'Lenora Jackson'; 'Estelle Fischer'; Mike Danyleiko (Mike Danyleiko); wrich@ucsd.edu; nfiner@ucsd.edu; higginsr@mail.nih.gov; 'Das, Abhik'; 'Poole, W. Kenneth'; Schaefer, Scott E.; 'Petrie, Carolyn'
Subject: FW: New SUPPORT Form

Fellow coordinator folks,

It was my intent that you guys give some feedback on the best way to do the supplemental data collection form (Supp11)

before it became anything official. Now that Betty has sent you all a copy, please look at it and think about the best way

to gather this data. As I will be away, please forward your comments to Angelita Hensman who will collate them and help

us come up with a best plan for the form.

Thank you.

Wade

Wade Rich, RRT-NPS

Clinical Research Administrator

Division of Neonatology

UCSD Medical Center

200 W Arbor Dr

San Diego, CA 92103-8774

619-543-5375

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Friday, May 06, 2005 6:15 AM
To: ahensman@wihri.org; mbball@leland.stanford.edu; grisbyca@email.uc.edu; ellen_hale@oz.ped.emory.edu; gaynelle.hensley@utsouthwestern.edu; Georgia E McDavid; auten002@mc.duke.edu; linda_reubens@urmc.rochester.edu; lucmille@iupui.edu; mcollins@peds.uab.edu; Nancy.Miller@utsouthwestern.edu; Nancy Newman; npeters@wfubmc.edu; monica.konstantino@yale.edu; ae5357@wayne.edu; rbridge@ucsd.edu; risa.demetrio@sharp.com; kathy.arnell@sharp.com; Reverett@med.miami.edu; brenda.H.Morris@uth.tmc.edu; cotte010@mc.duke.edu; crosen@mednet.swmed.edu; vanmeurs@leland.stanford.edu; kurt.schibler@cchmc.org; alaptook@wihri.org; Jobea0@chmcc.org; bpoindex@iupui.edu; edward.donovan@chmcc.org; jlemons@iupui.edu; moshea@wfubmc.edu; sshankar@med.wayne.edu; sduara@miami.edu; susie.buchter@oz.ped.emory.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; Vineet.bhandari@yale.edu; vivek.Narendran@cchmc.org; Walid.Salhab@utsouthwestern.edu; (b) (6) com; Lenora Jackson; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD
Cc: wrich@ucsd.edu; nfiner@ucsd.edu; higginsr@mail.nih.gov; Das, Abhik; Poole, W. Kenneth; Petrie, Carolyn; Schaefer, Scott E.; Auman, Jeanette O.
Subject: New SUPPORT Form

Attached is a Technical Memo, new SUPPORT study form(SUPP11) and corresponding MOP Chapter 16 for this form. This form is intended to be completed **if an infant is on support after day 14.**

Please let us know if you have questions about this material.
Thanks.
Betty <<SUP02.doc>> <<SUPP11 5-5-05 .doc>> <<Chapter 16.doc>>

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

From:	Neil Finer
To:	"Duara, Shahnaz"; wcarlo@peds.uab.edu; edward.donovan@cchmc.org; poo@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; "Michele Walsh"
Cc:	adas@rti.org
Subject:	RE: Growth May 10.doc
Date:	Tuesday, May 10, 2005 6:42:24 PM

Hi Shahnaz
These look fine - the aims 4 thru 7 are also a part of our secondaries not as specifically stated.
Hypothesis 3 - looks obvious and not related to SUPPORT. Hopefully we have few of these.
Neil

-----Original Message-----
From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Tuesday, May 10, 2005 2:38 PM
To: wcarlo@peds.uab.edu; edward.donovan@cchmc.org; poo@rti.org; nfiner@UCSD.edu; Rosemary Higgins; Michele Walsh
Cc: adas@rti.org
Subject: Growth May 10.doc

Hi,

Cristina has re-worked the Hypothesis and Specific Aims for the Growth secondary for SUPPORT, incorporating the feed-back she got - this was the area where most of the suggestions were. Please take a look and let me know what you think, since she is anxious to move the protocol forward.
SUPPORT
Thanks
Shahnaz
<<Growth May 10.doc>>

From: Duara, Shahnaz
To: wcarlo@peds.uab.edu; edward.donovan@cchmc.org; poo@rti.org; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Michele Walsh
Cc: adas@rti.org
Subject: Growth May 10.doc
Date: Tuesday, May 10, 2005 5:38:10 PM
Attachments: Growth May 10.doc

Hi,

Cristina has re-worked the Hypothesis and Specific Aims for the Growth secondary for SUPPORT, incorporating the feed-back she got - this was the area where most of the suggestions were. Please take a look and let me know what you think, since she is anxious to move the protocol forward.

Thanks
Shahnaz
<<Growth May 10.doc>>

A. Primary Hypothesis:

1. Infants in the low oxygen saturation group (85-89) will have better in-hospital growth and better growth at 18-22 months corrected age.

B. Secondary Hypothesis:

1. Postnatal growth will be better in infants who spend > 50% of the time with daily median oxygen saturation between 85% -95% while on supplemental oxygen, independent of saturation randomization group.

2. Infants with BPD (oxygen at 36 weeks) will have poorer growth than infants without BPD, independent of group of saturation randomization.

3. Infants with NEC $\geq$ Bell Stage 2 will have poorer growth, independent of group of saturation randomization.

C. Specific Aims:

1. To determine growth (wt, HC, length) in infants randomized within the SUPPORT trial to low and high saturation arms, from birth to discharge and again at 18-22 months corrected age.

2. To determine the percentage of infants with growth < 10 percentile at discharge.

3. To determine the percentage of infants with growth < 10 percentile at 18-22 months corrected age.

4. To determine the proportion of time spent with oxygen saturation <85% and >95%.

5. To determine the proportion of time spent with oxygen saturation 85-95%.

5. To determine the proportion of infants with median oxygen saturation < 85 % - $\geq$ 75%.

6. To determine the proportion of infants with median oxygen saturation < 75%.

7. To determine the proportion of infants with median oxygen saturation > 95%.

8. To determine in-hospital growth velocity.

9. To determine growth velocity from discharge to follow up, at 18-22 months corrected age.

From: Higgins, Rosemary (NIH/NICHD)
To: wrich@ucsd.edu
Subject: RE: Support SAEs
Date: Tuesday, May 10, 2005 2:00:00 PM

Thanks
Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Tuesday, May 10, 2005 1:57 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: Support SAEs

Sorry, we did not have them yet when I sent the forms. Identified versions attached.
Wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, May 10, 2005 9:35 AM
To: wrich@ucsd.edu; 'Hastings, Betty J.'
Subject: RE: Support SAEs

Wade
Can you add the study identifier to the forms?
Thanks
Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Tuesday, May 10, 2005 12:13 PM
To: 'Hastings, Betty J.'; Higgins, Rosemary (NIH/NICHD)
Subject: Support SAEs

Twin SAEs.
Wade

Wade Rich, RRT-NPS
Clinical Research Administrator
Division of Neonatology
UCSD Medical Center
200 W Arbor Dr
San Diego, CA 92103-8774
619-543-5375
pgr 290-(b) (6)

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support SAEs
Date: Tuesday, May 10, 2005 1:57:42 PM
Attachments: TomaMedwatch.pdf
TombMedwatch.pdf

Sorry, we did not have them yet when I sent the forms. Identified versions attached.
Wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, May 10, 2005 9:35 AM
To: wrich@ucsd.edu; 'Hastings, Betty J.'
Subject: RE: Support SAEs

Wade
Can you add the study identifier to the forms?
Thanks
Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Tuesday, May 10, 2005 12:13 PM
To: 'Hastings, Betty J.'; Higgins, Rosemary (NIH/NICHD)
Subject: Support SAEs

Twin SAEs.
Wade

Wade Rich, RRT-NPS
Clinical Research Administrator
Division of Neonatology
UCSD Medical Center
200 W Arbor Dr
San Diego, CA 92103-8774
619-543-5375
pgr 290-(b) (6)

SUPPORT TRIAL - NICU

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence #

A. PATIENT INFORMATION

1. Patient Identifier: toma (b) (6) In confidence
2. Age at Time of Event: or Date of Birth: (b) (6)
3. Sex: ☑ Female ☐ Male
4. Weight: ____ lbs or 0.840 ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: ____ *(mo/day/yr)*
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☐ Disability
- ☐ Congenital Anomaly
- ☑ Required Intervention to Prevent Permanent Impairment/Damage
- ☐ Other: ____

3. Date of Event *(mo/day/year)*: (b) (6)
4. Date of This Report *(mo/day/year)*: (b) (6)

5. Describe Event or Problem

25 5/7 wk premature female twin A doing well on DOL 2. On Nasal Continuous Positive Airway Pressure. Neonatal Fellow called to bedside at 20:30 on (b) (6) for acute deterioration, increased oxygen requirement. Breath sounds decreased on the right side. Transillumination showed right sided pneumothorax. Chest tube placed. Infant intubated and placed on SIMV. Infant remains stable after procedures.

6. Relevant Tests/Laboratory Data, Including Dates

Arterial Blood Gas prior to intubation:
pH 7.01 PCO2 84 PO2 61

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
#1
#2

2. Dose, Frequency & Route Used
#1
#2

3. Therapy Dates *(If unknown, give duration) from/to (or best estimate)*
#1
#2

4. Diagnosis for Use *(Indication)*
#1
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # *(if known)*
#1
#2

7. Exp. Date *(if known)*
#1
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# *(For product problems only)*

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model #
Lot #
Catalog #
Expiration Date *(mo/day/yr)*
Serial #
Other #
5. Operator of Device
☐ Health Professional
☐ Lay User/Patient
☐ Other:
6. If Implanted, Give Date *(mo/day/yr)*
7. If Explanted, Give Date *(mo/day/yr)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? *(Do not send to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mo/day/yr)*
11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

1. Name and Address
Wade Rich
UCSD Medical Center 200 W Arbor Dr
San Diego California 92103
United States wrich@ucsd.edu
Phone # 858-543-5375

2. Health Professional? ☑ Yes ☐ No
3. Occupation: Other Health Professional
4. Also Reported to:
☐ Manufacturer
☑ User Facility
☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

SUPPORT TOTAL = 10470

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence #

A. PATIENT INFORMATION

1. Patient Identifier: (b) (6) In confidence
2. Age at Time of Event: or Date of Birth: (b) (6)
3. Sex: ☑ Female ☐ Male
4. Weight: 0970 or ____ lbs ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: ____ *(mo/day/yr)*
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☐ Disability
- ☐ Congenital Anomaly
- ☑ Required Intervention to Prevent Permanent Impairment/Damage
- ☐ Other: ____

3. Date of Event *(mo/day/year)*: (b) (6)
4. Date of This Report *(mo/day/year)*: (b) (6)

5. Describe Event or Problem

25 5/6 wk premature infant with RDS doing well on DOL 2 on NCPAP. Fellow called to bedside at 02:15 on (b) (6) for desaturations and increasing oxygen requirements. Infant was found to be grunting on NCPAP of 7. Infant was intubated without difficulty. Post intubation chest x-ray showed a right sided pneumothorax. A 10 Fr. chest tube was placed. Infant remains stable after procedures.

6. Relevant Tests/Laboratory Data, Including Dates

ABG prior to intubation:
pH 7.14 PCO2 68 PO2 56.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
#1
#2

2. Dose, Frequency & Route Used
#1
#2

3. Therapy Dates *(If unknown, give duration)* from/to *(or best estimate)*
#1
#2

4. Diagnosis for Use *(Indication)*
#1
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # *(if known)*
#1
#2

7. Exp. Date *(if known)*
#1
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# *(For product problems only)*

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State

4. Model # | Lot #
Catalog # | Expiration Date *(mo/day/yr)*
Serial # | Other #

5. Operator of Device
☐ Health Professional
☐ Lay User/Patient
☐ Other: ____

6. If Implanted, Give Date *(mo/day/yr)*
7. If Explanted, Give Date *(mo/day/yr)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

10. Device Available for Evaluation? *(Do not send to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mo/day/yr)*

11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

1. Name and Address
Wade Rich
UCSD Medical Center 200 W Arbor Dr.
San Diego California 92103
United States wrich@ucsd.edu

Phone # 619-543-5375

2. Health Professional? ☑ Yes ☐ No
3. Occupation: Other Health Professional
4. Also Reported to:
☐ Manufacturer
☑ User Facility
☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

From: Wade Rich
To: "Hastings, Betty J."; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support SAEs
Date: Tuesday, May 10, 2005 12:14:43 PM
Attachments: TomaMedwatch.pdf
TombMedwatch.pdf

Twin SAEs.
Wade

Wade Rich, RRT-NPS
Clinical Research Administrator
Division of Neonatology
UCSD Medical Center
200 W Arbor Dr
San Diego, CA 92103-8774
619-543-5375
pgr 290(b) (6)

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence #

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: / Date of Birth:	3. Sex	4. Weight
toma In confidence	or _____ Date of Birth: (b) (6)	☑ Female ☐ Male	_____ lbs 0.840 kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: _____ *(mo/day/yr)*
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☐ Disability
- ☐ Congenital Anomaly
- ☑ Required Intervention to Prevent Permanent Impairment/Damage
- ☐ Other: _____

3. Date of Event *(mo/day/year)*	4. Date of This Report *(mo/day/year)*
(b) (6)	(b) (6)

5. Describe Event or Problem

25 5/7 wk premature female twin A doing well on DOL 2. On Nasal Continuous Positive Airway Pressure. Neonatal Fellow called to bedside at 20:30 on (b)(6) for acute deterioration, increased oxygen requirement. Breath sounds decreased on the right side. Transillumination showed right sided pneumothorax. Chest tube placed. Infant intubated and placed on SIMV. Infant remains stable after procedures.

6. Relevant Tests/Laboratory Data, Including Dates

Arterial Blood Gas prior to intubation:
pH 7.01 PCO2 84 PO2 61

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
#1
#2

2. Dose, Frequency & Route Used	3. Therapy Dates *(If unknown, give duration)* from/to *(or best estimate)*
#1	#1
#2	#2

4. Diagnosis for Use *(Indication)*
#1
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # *(if known)*	7. Exp. Date *(if known)*
#1	#1
#2	#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# *(For product problems only)*

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Type of Device

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mo/day/yr)*	☐ Health Professional ☐ Lay User/Patient
Serial #	Other #	☐ Other:

6. If Implanted, Give Date *(mo/day/yr)*	7. If Explanted, Give Date *(mo/day/yr)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

10. Device Available for Evaluation? *(Do not send to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mo/day/yr)*

11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

1. Name and Address
Wade Rich
UCSD Medical Center 200 W Arbor Dr
San Diego California 92103
United States wrich@ucsd.edu

Phone # 858-543-5375

2. Health Professional?	3. Occupation	4. Also Reported to:
☑ Yes ☐ No	Other Health Professional	☐ Manufacturer ☑ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

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SUPPORT PLEASE MED

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Internet Submission - Page 1

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence #

A. PATIENT INFORMATION

1. Patient Identifier: tomb (In confidence)
2. Age at Time of Event: or Date of Birth: (b) (6)
3. Sex: ☑ Female ☐ Male
4. Weight: 0970 lbs or kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
- ☐ Death: (mo/day/yr)
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☐ Disability
- ☐ Congenital Anomaly
- ☑ Required Intervention to Prevent Permanent Impairment/Damage
- ☐ Other:

3. Date of Event *(mo/day/year)*: (b) (6)
4. Date of This Report *(mo/day/year)*: (b) (6)

5. Describe Event or Problem

25 5/6 wk premature infant with RDS doing well on DOL 2 on NCPAP. Pellow called to bedside at 02:15 on (b) (6) for desaturations and increasing oxygen requirements. Infant was found to be grunting on NCPAP of 7. Infant was intubated without difficulty. Post intubation chest x-ray showed a right sided pneumothorax. A 10 Fr. chest tube was placed. Infant remains stable after procedures.

6. Relevant Tests/Laboratory Data, Including Dates

ABG prior to intubation:
pH 7.14 PCO2 68 PO2 56.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*: #1 / #2
2. Dose, Frequency & Route Used: #1 / #2
3. Therapy Dates *(If unknown, give duration)* from/to (or best estimate): #1 / #2
4. Diagnosis for Use *(Indication)*: #1 / #2
5. Event Abated After Use Stopped or Dose Reduced? #1 ☐ Yes ☐ No ☐ Doesn't Apply; #2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot # *(if known)*: #1 / #2
7. Exp. Date *(if known)*: #1 / #2
8. Event Reappeared After Reintroduction? #1 ☐ Yes ☐ No ☐ Doesn't Apply; #2 ☐ Yes ☐ No ☐ Doesn't Apply
9. NDC# *(For product problems only)*
10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date *(mo/day/yr)* / Serial # / Other #
5. Operator of Device: ☐ Health Professional ☐ Lay User/Patient ☐ Other:
6. If Implanted, Give Date *(mo/day/yr)*
7. If Explanted, Give Date *(mo/day/yr)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? *(Do not send to FDA)* ☐ Yes ☐ No ☐ Returned to Manufacturer on: (mo/day/yr)
11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER *(See confidentiality section on back)*

1. Name and Address: Phone # 619-543-5375

Wade Rich
UCSD Medical Center 200 W Arbor Dr.
San Diego California 92103
United States wrich@ucsd.edu

2. Health Professional? ☑ Yes ☐ No
3. Occupation: Other Health Professional
4. Also Reported to: ☐ Manufacturer ☑ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (9/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT secondaries: Hintz and Stevens
Date: Thursday, May 05, 2005 3:49:33 PM

When I talked to Dr. Stevens this morning he indicated that the first interview would be done (before discharge) by the Network coordinators and the telephone interviews (and tracking) may be done by Rochester. He wasn't quite sure how it would be done.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 05, 2005 3:45 PM
To: Hastings, Betty J.
Subject: RE: SUPPORT secondaries: Hintz and Stevens

That is fine - I don't think the FU folks reviewed it because the suggestion was made that all of phone contacts be done in Rochester.
thanks Rose

-----Original Message-----
From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Thursday, May 05, 2005 3:44 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT secondaries: Hintz and Stevens

He was asking if we can provide them with listings of the infants to contact (like we do for some of the other studies) and I told him sure. Since this is a follow-up study, I may just pass the protocol on to Beth. Thanks.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 05, 2005 3:40 PM
To: Hastings, Betty J.
Subject: RE: SUPPORT secondaries: Hintz and Stevens

I think most if not all of the sites will participate in pulmonary outcomes. For the MRI- Brown and Wake Forest are still up in the air, but I think everyone else is participating. I believe you are correct - the pulmonary outcomes is follow up, but the Rochester site has agreed to do the tracking
- the infants will be seen at the sites at 18-22 months.
Thanks
Rose

-----Original Message-----
From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Thursday, May 05, 2005 3:37 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT secondaries: Hintz and Stevens

Rose, Do you know what sites will be participating in the MRI Secondary?

I was thinking of sending this protocol as well as the follow-on (Pulmonary Outcomes) out to the sites tomorrow. I was also wondering, shouldn't this follow-on Pulmonary be considered a follow-up study since most of the data is collected after discharge (6-12 months and 18-22 months).
Thanks.
Betty

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 05, 2005 11:32 AM
To: Hastings, Betty J.
Subject: RE: SUPPORT secondaries: Hintz and Stevens

If they are ready for the IRBs, it is fine.
Thanks
Rose

-----Original Message-----
From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Thursday, May 05, 2005 11:31 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT secondaries: Hintz and Stevens

Thanks Rose. I guess I can go ahead and have the protocols posted on the Web. I talked to Dr. Stevens this morning about the Pulmonary secondary.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 05, 2005 11:29 AM
To: Duara, Shahnaz; Hastings, Betty J.
Cc: Petrie, Carolyn
Subject: RE: SUPPORT secondaries: Hintz and Stevens

Shahnaz,
Betty is working on them and will send them to the sites when ready for IRB. Thanks Rose

-----Original Message-----
From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Thursday, May 05, 2005 11:04 AM
To: Hastings, Betty J.
Cc: Higgins, Rosemary (NIH/NICHD); Petrie, Carolyn
Subject: SUPPORT secondaries: Hintz and Stevens

Hi Betty,

Are the SUPPORT secondaries from Hintz and Stevens ready for IRB? Are they going to go up on the web-site soon?

Let me know
Shahnaz

From: Higgins, Rosemary (NIH/NICHD)
To: Raju, Tonse (NIH/NICHD) [E]
Subject: Tim Stevens
Date: Thursday, May 05, 2005 12:14:00 PM

Hi Raju,
Tim Stevens from Univ. Rochester had applied for a K23 for pulmonary follow up as a secondary study to the SUPPORT trial. This study has been approved and is going forward in the Neonatal Research network. We will provide site related capitation costs. I know that he got a (b) (5) on the K23 score -- the cutoff last time was 160. DO you know if he is reapplying?? Dale Phelps had told me awhile ago that he (b) (5) .
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Hastings, Betty J.
To: timothy_stevens@urmc.rochester.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT Pulmonary Outcomes
Date: Tuesday, May 03, 2005 1:49:37 PM

Dr. Stevens,

I received the SUPPORT Trial Follow-on Study Protocol and questionnaires from Dr. Higgins this morning. I have a few questions about how things should proceed as far as the Data Center is concerned.

- It looks like all of the questionnaires have been developed (using the Tucson Respiratory Study) so it doesn't look like we will need to develop any additional forms for this study, is this correct?
- It appears that the first interview (Family and Environmental Risk Factors for Wheezing) will be completed by the NICHD Network Centers. Will this information be sent to the Data Center or is this something that will be sent to Rochester for keying? If it is coming to the data center, we will need to develop data entry software for keying at the sites.
- For the telephone interviews, if the Rochester research staff will be conducting these, will this data also be keyed at the Rochester site? If they are being conducted at the individual Network centers, should the Data Center develop data entry software for keying at the sites or will these hard copy questionnaires be sent to Rochester?
- On page 11 of the protocol, you stated: ***"To facilitate tracking and record keeping, Dr. Stevens will design and write a database to track enrolled patients and their contact information, next scheduled interview, and record answers to phone interview questions".*** How will the Data Center obtain this information?
- On page 13 of the protocol, you stated: ***"All analyses will be performed in conjunction with the Research Triangle Institute (RTI, North Carolina), the biostatistical support group for the NICHD Neonatal Network".*** How will the Data Center obtain this information?

I hope you don't mind all the questions, but I'm not sure how to move forward without clarification. Thanks so much for your help.

Betty

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

From: Higgins, Rosemary (NIH/NICHD)
To: Tyson, Jon E; Michael Cotten
Subject: RE: concurrent OB trials
Date: Tuesday, May 03, 2005 12:52:00 PM

For randomized trials, the party line has usually been that participation in multiple studies is OK provided the primary outcomes are not the same (for instance inositol + SUPPORT). I would suggest you send Jon and outline of the study for final determination.
Thanks
Rose

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]
Sent: Tuesday, May 03, 2005 12:36 PM
To: Michael Cotten
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: RE: concurrent OB trials

I got deep into the generic issue. While I would like to see an abstract of this specific study, I would think the Network wouldn't need to stratify, and I don't see why your center couldn't participate. Do you agree Rose?

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

From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Tuesday, May 03, 2005 11:26 AM
To: Tyson, Jon E
Cc: goldb008@mc.duke.edu
Subject: RE: concurrent OB trials

thanks for your ample thoughts Jon....I believe the OB study contemplated by Duke OBs (and UNC and UT San Antonio) involves aggressive dental care vs standard...I think recording study enrollment is a reasonable option. I'm cc'ing Ron on this as he and I will be talking to OB researchers at Duke in the near future about this study.I"ll look forward to hearing the subcommittee's comments before we agree to have Duke as a site in the OB study.

mc

C. Michael Cotten, MD
Assistant Clinical Professor of Pediatrics
Clinical Research Director, Duke Neonatology
Director Special Care Nursery, Durham Regional Hospital
Box 3179 DUMC
Durham, NC 27710
(919) 681-6025
fax: (919) 681-6065
pager: (919) 970-(b) (6)

"Tyson, Jon E"
<Jon.E.Tyson@uth.tmc.edu>

05/03/2005 12:04 PM

To: "Michael Cotten" <cotte010@mc.duke.edu>
cc: "Dale Phelps" <dale_phelps@urmc.rochester.edu>, "Lemons Jim \(E-mail\)" <jlemons@iupui.edu>, "Neil Finer" <nfiner@ucsd.edu>, "Poole Kenneth \(E-mail\)" <poo@rti.org>, "Abhik Das" <adas@rti.org>, <moshea@wfubmc.edu>, "k poole" <poo@rti.org>, <higginsr@mail.nih.gov>
Subject: RE: concurrent OB trials

You raise a level of complexity that to my knowledge has been only briefly discussed on a few occasions in Network meetings.

For whatever it is worth, my view had been that concurrent Ob trials are not much of a threat to the validity of Neonatal Network trials because:

1) Randomization of the variable under investigation (e.g., the phototherapy regimen) is the primary safeguard against important baseline differences (to use an example you note, say maternal Mg Rx) that could affect the primary outcome variable (death or impairment); stratification is a less important factor;
2) With or without stratification, the risk of important imbalances is reduced in trials of the size the Network does;
3) The possibility of important baseline imbalances (in say, imbalances between phototherapy groups with respect to maternal Mg Rx) exists whether or not there is a concurrent maternal trial (e.g., the BEAM Trial). Random assignment of mothers to Mg within the participating centers would not increase this likelihood of baseline differences. It might even reduce it (e.g. by reducing variability between centers and thereby increase the signal to noise ratio);
4) In any trial, there may be a large number of variables that could affect outcome and it would not be feasible to stratify for many of them. Conventional wisdom is to stratify for only a few important variables at enrollment to avoid undue complexity in conducting the trial and reduce the risk of unfilled cells (say, only one patient enrolled with an unusual combination of stratifying variables);
5) As long as the variable being randomized is within the range of conventional practice (e.g. as I argued in the case of the proposed trial at Duke, different levels of light exposure), large artifacts are not likely to result. (I should add that some statisticians argue against the use of stratification at enrollment and argue for statistical adjustment for unbalanced variables in the analysis. However, it is possible that post hoc adjustment to balance one factor may inadvertently imbalance another that was balanced before the adjustment. So posthoc adjustments might move the Relative Risk farther from --rather closer--to the correct value.)

That said, there is another issue. Whatever approach we use for stratification, it is possible that the generalizability of the findings (as opposed to their validity) in Network trials will be affected by the results of the maternal trials. If say, the results of the BEAM trial prompt a systematic increase or decrease in the use of Mg, the generalizability of the phototherapy trial for future practice would change if for some reason the effect of phototherapy regimen on outcome is altered by antenatal Mg Rx. We would be best positioned to assess whether this effect is changed if we had stratified for maternal Mg group or at least recorded whether the infants were in the trial. If the trial results were compelling, we could then determine whether there was an interaction between the intervention tested in the Neonatal Network and the intervention tested in the MFM Network trial.

To sum up, I would think we should continue what we are doing (conduct large trials and stratify for a modest number of variables) but to record for individual infants whether they were enrolled in an MFM trials that may change clinical practice. If follows that we should seriously consider stratifying for the treatment group in the MFM Trial if we think a) it is very likely that the MFM trial will change clinical practice (whichever group has the best outcome); b) there is good reason to think the intervention may affect the primary outcome of the Network trial, c) a substantial proportion of infants in the Neonatal Network trial are likely to come from mothers enrolled in the MFM Network trial, and d) we could stratify for MFM treatment group (say Group A or Group B) without much chance of compromising blinding what MFM intervention was given or biasing the recording of outcome data.

I'm interested in what other members of the subcommittee would think and will forward this to them as well.

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

From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Tuesday, May 03, 2005 8:42 AM
To: Tyson, Jon E
Cc: Ronald N Goldberg
Subject: concurrent OB research

Hi Jon...

Duke OB is interested in participating in an NIH sponsored, 3 center intervention study of oral hygiene to prevent prematurity and improve neonatal outcomes...we"ve been asked to do the f/up piece...

question:

1) do maternal intervention studies require review by the concurrent research subcommittee and stratification of randomization (such as progesterone, Mg, antenatal steroid repeat dosing, fetal oximetry) for NRN trials of neonatal interventions?
I figure some of the maternal interventions may actually have impact on neonatal outcomes....

mc

C. Michael Cotten, MD
Assistant Clinical Professor of Pediatrics
Clinical Research Director, Duke Neonatology
Director Special Care Nursery, Durham Regional Hospital
Box 3179 DUMC
Durham, NC 27710
(919) 681-6025
fax: (919) 681-6065
pager: (919) 970-(b) (6)

From: Susan Hintz
To: bkh@rti.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]; neil finer; dstevenson@stanford.edu; poo@rti.org
Subject: SUPPORT Neuroimaging Secondary
Date: Friday, April 29, 2005 3:19:44 PM
Attachments: NeuroimageSUPPORTFinal.doc
SUPP_consent_embedded_example.doc
SUPP_MRI_standalone_example.doc

Hello all,

Attached is the SUPPORT Neuroimaging Secondary and sample consents for your review. One of the consent forms is for a "stand alone" option (i.e., enrolling in the secondary separately from SUPPORT), and the other is for an "embedded" option (i.e., obtaining consent for both at the same time). I believe that the "embedded" option will be best for those centers that currently (or WILL very soon) perform brain MRI as the routine near-term neuroimaging exam.

I have also been developing some screening/data form drafts - I will send those to Betty and all of you on Monday or Tuesday. I have sent Neil and Rose the draft of the central MRI scoring form that I have put together with Pat Barnes - Betty, I will send that to you as well because I would like your opinion and help on the best lay-out options.

As soon as you have reviewed these documents and feel it is appropriate, RTI or I can send the protocol to the centers and then RTI can poll the centers to ascertain which will actually be able to participate.

Thank you for all your support (no pun intended).

Susan
--
Susan R. Hintz, M.D.
Assistant Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

NEUROIMAGING AND NEURODEVELOPMENTAL OUTCOME: A SECONDARY TO SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL (SUPPORT)

A. Abstract/Statement of Problem

Cranial ultrasound (US) is currently used for brain imaging in the extremely preterm population, but this modality cannot detect subtle brain injury that may be responsible for later neuromotor and cognitive delay. Magnetic resonance imaging (MRI) can identify brain structural abnormalities and white matter injury better than cranial US. The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) will evaluate if permissive ventilation strategies and lower SpO_2 targets will result in increased survival without bronchopulmonary dysplasia (BPD) and increased survival without retinopathy of prematurity (ROP) among 24-27+6/7 week EGA infants. It is not known whether differing ventilation and oxygenation management approaches could be associated with brain injury, particularly white matter injury. Extremely premature infants are at very high risk for neuromotor and neurodevelopmental impairment, including cerebral palsy and severe cognitive impairment. Whether MRI can predict neurodevelopmental outcome better than cranial US among preterm infants is not yet known. In this secondary study to SUPPORT, specifically timed cranial US and brain MRI will be obtained. **We will test the hypothesis that ventilation and oxygenation strategies in SUPPORT will not be associated with an increase in death or brain injury (Grade 3/4 IVH by cranial US at 4-14 days ("early cranial US") or 35-42 weeks ("late cranial US"), abnormal brain MRI at 35-42 weeks). We will also use neurodevelopmental follow-up data at 18-22 months corrected age to assess comparative and combined predictive capabilities of these neurodiagnostic modalities.** The NICHD Neonatal Research Network is uniquely positioned to embark upon such a project, which would be the first multicenter, prospective study to investigate these important questions.

B. Objective

This secondary is a prospective study of cranial US at 4-14 days ("early") and 35-42 weeks postmenstrual age (PMA) ("late"), and brain MRI at 35-42 weeks PMA among infants enrolled in SUPPORT. We will evaluate and compare the capabilities of early and late cranial US and brain MRI to predict neuromotor and neurodevelopmental outcome at 18-22 months corrected age. We will also determine if ventilatory or oxygen saturation interventions are associated with differences in the outcomes of death or abnormal neuroimaging findings (death/grade 3/4 IVH on "early" US, death/grade 3/4 IVH on "late" US, death/PVL, death/abnormal MRI) among patients enrolled in this secondary.

C. Hypotheses

- Multivariate modeling will demonstrate that conventional brain MRI at 35-42 weeks PMA will be superior to cranial US in predicting neurodevelopmental outcome at 18-22 months corrected age.
- There will be insufficient evidence to reject the null hypothesis that no differences exist in the frequency of Death/Grade 3/4 IVH or Death/PVL on early or late US

between Low and High SpO_2 groups (within each randomized ventilation strategy), or between Early CPAP and Control ventilation groups (within each randomized oxygenation strategy).

- There will be insufficient evidence to reject the null hypothesis that the frequency of Death/abnormal brain MRI at 35-42 weeks postmenstrual age (PMA) is not different between Low and High SpO_2 groups (within each randomized ventilation strategy), or between Early CPAP and Control ventilation groups (within each randomized oxygenation strategy).

D. Specific Aims

1) To obtain consistently performed, timed and interpreted neuroimaging studies in extremely preterm infants enrolled in SUPPORT:
    a. cranial US at 4-14 days of age
    b. cranial US at 35-42 weeks PMA
    c. MRI at 35-42 weeks PMA
2) To compare early and late US and MRI findings between Low and High SpO_2 groups, and between Early CPAP and Control ventilation groups.
3) To utilize the NICHD Neonatal Research Network follow-up programs to assess neurodevelopmental outcomes at 18-22 months corrected age, as described in SUPPORT.
4) To examine the independent associations of neuroimaging findings with neurodevelopmental outcomes through predictive modeling.
    a. Regression models will assess the absolute and relative value of early and late cranial US, and brain MRI, alone and in combination with traditional risk factors, to predict both abnormal and normal neurodevelopmental outcome at 18-22 months.
    b. Through stepwise regression modeling, we will also assess the value of neuroimaging findings, alone and in combination, in predicting neurodevelopmental outcomes over and above the value of early risk factors or early and in-hospital risk factors alone.

E. Background, Significance and Rationale

The importance of an advanced neuroimaging component to SUPPORT:

SUPPORT will be the largest randomized controlled trial of ventilatory and oxygen saturation target management in extremely premature infants to date. Although the primary outcomes for SUPPORT focus on survival without BPD and survival without ROP, it will be crucial to evaluate the potential impact of study interventions on both neuroimaging findings and neurodevelopmental outcomes. One possible concern could be that lower oxygenation parameters and less aggressive ventilatory management may be associated with a higher incidence of brain white matter injury. This position might be extrapolated from earlier observations in preterm infants (1,2), and from studies of near-term and term hypoxic brain injury.

Other investigations suggest that more aggressive ventilation strategies leading to hypocapnia may place the premature infant at higher risk for reduced cerebral blood flow (CBF) and subsequent white matter injury. The CBF-carbon dioxide reactivity observed in adult animals may be blunted or incomplete in newborn and preterm

animals (3,4). Nevertheless, several clinical case series of preterm infants have demonstrated strong associations of hypocapnia with significant abnormal findings on brain imaging and with adverse neurodevelopmental outcome (5-8), although other important risk factors were also identified.

At the very least, neuroimaging abnormalities in preterm infants are likely to be the result of a multifactorial process. Emerging evidence points to the unique vulnerability of the preterm infant brain in several respects. Low blood flow to the cerebral white matter and impaired cerebrovascular autoregulation in premature infants (9-11) may make subtle brain ischemic injury more likely. Coupled with this tendency to ischemic injury, is the vulnerability of developing oligodendroglial cells to damage (see below). Finally, it is possible that effects of exposure to *in utero* infection, frequently suspected in extremely preterm infants, may potentiate brain cellular injury caused by mild to moderate ischemia (12,13).

Summary: Given the interventions to be undertaken in SUPPORT, and the complexity and multifactorial nature of the development of white matter injury in the premature brain, advanced neuroimaging could be a critical component to the trial. This secondary to SUPPORT will provide important additional information to investigators with respect to the impact of respiratory management on subtle brain injury.

The need to investigate emerging brain imaging modalities:

Premature infants are at high risk for neuromotor and neurodevelopmental impairment. Recent reported frequencies of cerebral palsy (CP) at 18-24 months corrected age range from 11-20%, and of cognitive delay range from 30-60% for the extremely low birth weight (ELBW) population (14-16). Yet, despite numerous investigations, the complete explanation of these impairments remains unclear. Correlation of specific neonatal factors, particularly neuroimaging findings, with adverse neuromotor and neurodevelopmental outcomes are frequently demonstrated. Many studies have emphasized the association of cranial US abnormalities including intraventricular hemorrhage (IVH) grades 3 and 4, periventricular leukomalacia (PVL) and ventricular dilatation with subsequent neurologic and cognitive impairment (14-20). Most investigators have found abnormalities on cranial US to be an independent risk factor for neuromotor abnormalities, but not necessarily for cognitive impairment.

However, severe cranial US abnormalities are not uniformly predictive of adverse neuromotor outcome in the premature population. In a study of perinatal correlates of neurologic impairment at 18-22 months corrected age among VLBW infants (20), only 52% of the infants with CP on follow-up had had severe cranial US abnormalities. This finding was in contrast to a 12% prevalence of severe cranial US abnormalities among matched controls without CP. In a neurodevelopmental follow-up study of ELBW infants in a multicenter, double masked, randomized controlled trial of indomethacin prophylaxis in preterms (TIPP), survival without neurosensory impairment was similar between treatment groups although incidence of grade 3 or 4 IVH on cranial US had been significantly reduced by treatment with indomethacin (21).

Smaller studies have investigated the capabilities of cranial US at term to predict CP among preterm infants, revealing a sensitivity of only approximately 60% (22,23). Other reports have indicated that cystic PVL may be detected in infants without previous

cranial US abnormalities at several months of age (24-26). These studies suggest that only certain types of brain injury may be detectable with cranial US, and that timing of studies may be crucial.

Summary: Cranial US, the imaging modality currently considered to be standard of care, may not detect subtle brain injury that is could be associated with later neuromotor or neurodevelopmental delay among ELBW infants.

MRI compared with cranial US to assess of brain injury and predict neurologic outcome

MRI provides a more complete and anatomically detailed evaluation of the neonatal brain. Several studies have compared the relative capabilities of US with MRI to detect brain injury among preterm infants in the newborn period. These reports concluded that MRI detects white matter injury better than HUS (27-29), and provides additional information regarding hemorrhage and cystic changes not noted by cranial US. Childs, et. al. assessed MRI and serial cranial US in both preterm and term infants, and concluded that MRI was more sensitive in identifying periventricular white matter lesions (30). However, neurodevelopmental outcome of the infants in those studies were not reported.

Few studies have compared MRI with cranial US to predict neurodevelopmental outcome among premature infants; those are small, primarily single-center efforts. Studies are difficult to compare due to variability of timing, imaging, and MRI scoring and interpretation. Valkama, et. al. (31) assessed MRI compared with cranial US performed at term in 51 VLBW, preterm infants (<34 weeks). Twelve infants were diagnosed with CP at 18 months corrected age. MRI parenchymal lesions predicted CP with 100% sensitivity and 79% specificity whereas US at term predicted CP with 67% sensitivity and 85% specificity. The authors concluded that MRI was the more reliable methodology. Stanford University researchers (see below "Preliminary Studies and Results") have completed a prospective study of neuroimaging among VLBW, preterm infants with neurodevelopmental follow-up at 18-22 months and 30 months corrected age (32). MRI at term predicted CP with superior sensitivity and positive predictive value compared with early cranial US.

Other studies have suggested the potential prognostic advantages of MRI compared with cranial US. Roelant-van Rijn and colleagues (33) studied 61 preterm infants with cranial US, and MRI within the first weeks of age and/or at term. MRI at term was found to be helpful in delineating internal capsule abnormalities, considered to be useful in predicting later hemiplegia. Other preliminary reports include that of Austin, et. al. (34) in which white matter injury on MRI at term among 93 VLBW infants was correlated with neuromotor abnormalities such as hypertonicity, hypotonicity, and motor delay at one year. In a very small group of premature infants <36 weeks, Miller, et. al. (35) showed that cerebellar hemorrhages detected by MRI, even if not associated with white matter injury, appeared to be associated with adverse neurodevelopmental outcome at 12 months.

There are potential criticisms to these studies. In most cases, MRI was compared with only "late" cranial US or only "early" US; a more complete comparison would include both early and late cranial US, demonstrating that the design of neuroimaging collection strategies in prospective studies is crucial. Many studies focus narrowly on neuromotor outcome, specifically the prevalence of CP, as outcome variables. A

broader neurodevelopmental assessment and comparison is warranted. Finally, all studies of MRI findings and correlation with neurodevelopmental outcomes in preterm infants thus far are small; it is therefore not possible to draw powerful conclusions, especially with regard to ELBW patients. In fact, the recently published "Practice Parameter: Neuroimaging of the Neonate" (36) failed to definitively recommend routine MRI for VLBW preterm infants in large part due to the lack of follow-up studies. But, many of the reports reviewed above were not available during the development of the "Practice Parameter".

Summary: MRI may be a powerful tool with which to predict adverse neuromotor outcome among preterm infants. However, timing of studies varies between published reports, and few have included prospective neurodevelopmental follow-up to compare the prognostic capabilities of MRI and US.

The importance of subtle white matter injury

Periventricular leukomalacia (PVL) has been categorized as "focal" and "diffuse" (37,38). Focal PVL has been described as the result of severe ischemic-necrotic injury and is located deep in the white matter. This type of injury may lead to the development of cystic changes or significant findings that can be detected by cranial US or conventional MRI. Diffuse PVL is thought to be the result of less severe injury, diffusely located in the white matter. The mechanism of diffuse PVL may be multifactorial, including: 1) mild to moderate ischemia due to decreases in cerebral blood flow consistent with impaired autoregulation, 2) vulnerability of immature oligodendroglial cells to ischemic injury and damage by chemical mediators, and 3) oligodendroglial cell susceptibility to injury and death after intraventricular hemorrhage due to creation of oxygen free radicals. The sensitivity of the immature oligodendroglial cells to cytokine-induced injury may help to provide a pathophysiologic explanation to the observations of increased prevalence of CP among infants born to mothers with chorioamnionitis, and among infants with early sepsis.

Diffuse PVL may be a clinically important and prevalent white matter injury in the preterm infant. Yet, diffuse PVL is unlikely to be seen by cranial US. Diffuse PVL may also be challenging to detect reliably on conventional MRI. However, in a study by Counsell et. al. (39), diffuse excessive high signal intensity (DEHSI) in the white matter of preterm infants at near-term was associated with higher apparent diffusion coefficient values on diffusion weighted MRI. This finding suggested that subtle injury, causing changes in cellular differentiation and probable preferential death of preoligodendrocytes, resulting in diffuse PVL (40), may be structurally visible in the form of DEHSI. The developmental significance for the preterm infant is not known. It is also important to note that not all subtle white matter injury is likely to be detectable even by MRI.

Summary: IVH and focal cystic PVL are detectable by conventional MRI or cranial US. However, subtle factors leading to diffuse or focal white matter injury may be detectable only by MRI. Such injury may have a substantial impact on normal white matter development and neuromotor outcome in the preterm infant; this question must be further studied in a large-scale, prospective manner.

Preliminary Studies and Results

A coordinated effort among neonatologists, radiologists, engineers, technicians and developmentalists has been in place at Lucile Packard Children's Hospital and the Lucas Center for Nuclear Magnetic Resonance at Stanford University. The objective of this group is to combine various fields of science to investigate novel, potentially clinically relevant neuroimaging approaches in term and preterm infants.

Cranial US vs. conventional MRI for prediction of CP in VLBW infants: Infants of <1250 grams and <30 weeks EGA were enrolled a prospective observational study of the capabilities of early cranial US compared with conventional MRI at near-term to predict CP at 18-22 months corrected age, and 30 months (32). Cranial US was obtained twice during the first two weeks of life, and the most abnormal findings were used for analysis. Conventional MRI and cranial US were scored with respect to size of hemorrhage, parenchymal involvement, and ventricular dilation. 62 infants participated in the study, with one excluded from analysis due to a later diagnosis of muscular dystrophy. The sensitivity and specificity of near-term MRI for predicting CP at 18-22 months were 71% and 91% respectively. The sensitivity of MRI for CP at 30 months of age increased to 86% with the specificity remaining high at 89%. Although the specificity was comparable to MRI, the sensitivity was only 29% at 18-22 months and 43% at 30 months.

This study, one of the largest prospective comparative neuroimaging studies of VLBW infants and neurodevelopmental outcome, supports the suggestion that conventional MRI may be superior to cranial US with respect to prediction of neuromotor abnormalities. There are limitations to this study, however. Comparison cranial US were performed early in the hospital course (<2 weeks), and no US contemporaneous with the MRI were routinely obtained. Recent studies by other investigators have also determined that, among VLBW infants, early cranial US poorly predicts non-cystic white matter injury on MRI at term (41). Previous reports by Valkama, et. al. (31) suggest that cranial US at term was also less than MRI at term. This study was limited by small sample size, with only 12 infants diagnosed with CP. Sample size considerations also restricted possibilities for multivariate modeling of outcomes, and meaningful analysis of Bayley Scales of Infant Development II scores.

Such limitations could be addressed by a prospective, multicenter study; both early and late cranial US would be obtained to evaluate the combined power of two US studies compared with MRI, and the projected large sample size would not restrict statistical analyses.

F. Research Design and Methods

1. Study Design: This secondary to SUPPORT is a prospective study of traditional (cranial US at 4-14 days and 35-42 weeks PMA) and advanced (MRI at 35-42 weeks PMA) neuroimaging with respect to SUPPORT randomized ventilation and oxygen saturation interventions. The capabilities of these neuroimaging modalities to predict neurodevelopmental outcome at 18-22 months corrected age will be assessed.

Perinatal, demographic and neonatal data will be collected as part of the ongoing NICHD Neonatal Research Network Survey of Morbidity and Mortality Among VLBW Infants (401-1500g) for the purposes of the study. Cranial US will be obtained at 4-14 days and at 35-42 weeks PMA, and, among participating centers, brain MRI will be

obtained within 7 days of late cranial US. For purposes of research outcomes, cranial US and MRI will be interpreted by central readers, but *clinical* interpretation will continue to be performed at individual Network sites. Central readers will be masked to patient identifiers, SUPPORT intervention, and clinical radiologists' interpretation. Detailed neuromotor and neurodevelopmental examinations will be undertaken at 18-22 months corrected age as part of the NICHD Cooperative Multicenter Network of Neonatal Intensive Care Units: Follow-Up of ELBW Infants (401-1000g), and per SUPPORT protocol.

Statistical analysis will include univariate and multivariate analyses to 1) assess the association of SUPPORT ventilation and oxygenation randomized treatment groups with neuroimaging, 2) evaluate the strength of independent associations of specific neuroimaging findings with neurodevelopmental outcomes and 3) develop predictive models.

2. Study Population

Inclusion Criteria

- Enrolled in the NICHD Neonatal Research Network SUPPORT study
- Cranial ultrasound can be obtained at 4-14 days of age and at 35-42 weeks PMA
- Brain MRI can be obtained per study specifications (see Appendix A) at 35-42 weeks PMA.
    - If MRI cannot be performed by 42 weeks due to subject clinical condition, the "late" cranial US used for study purposes should also be delayed so that cranial US is within 7 days of the brain MRI.

Exclusion Criteria

- Patient unlikely or family unwilling to participate in neurodevelopmental assessment at 18-22 month corrected age
- Presence of known or suspected congenital anomalies including:
    - ➤ Chromosomal anomalies
    - ➤ Complex congenital heart disease (PDA, small muscular VSD or PFO are NOT considered to be congenital heart disease for the purposes of this study)
    - ➤ Congenital infection (TORCH, untreated maternal HIV, syphilis)
- Lack of informed consent
- Patient is likely to be discharged or transferred by 35 weeks PMA to a facility where MRI per study specifications is not available.

Enrollment of Subjects

Screening: Each participating center will be responsible for devising a screening strategy to identify all potential participants using the study inclusion and exclusion criteria. Timing of consent will be left to individual centers. However, identification of patients should occur before 14 days in centers where routine US would be likely be performed later. In addition, some centers, particularly those in which MRI is the standard-of-care near-term neuroimaging method, may wish to incorporate consent for this secondary in their initial SUPPORT consent form.

Informed consent: Each participating center will follow procedures for developing informed consents as set out by the local Institutional Review Board (IRB). It is

expected that the parents of all eligible infants will be approached to participate in this secondary study at participating centers.

Eligible infants not enrolled: The reasons for non-enrollment will be documented. Short- and long-term outcomes of eligible infants not enrolled in this study will be documented as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality in VLBW Infants (Generic Data Base (GDB)) and, if enrolled, as part of the ongoing NICHD Neonatal Research Network ELBW neurodevelopmental follow-up study.

No MRI obtained for infants enrolled in the MRI portion of the study: An important objective of this secondary requires acquisition of MRI at 35-42 weeks PMA; it is crucial that each participating center make this a priority. However, if the patient is medically unstable during the entire 35-42 week PMA period, an MRI will not be obtained during that period. In this case, the MRI MAY BE DELAYED beyond 42 weeks, however LATE CRANIAL US USED FOR STUDY PURPOSES SHOULD ALSO BE DELAYED so that MRI and US are obtained within 7 days of each other.

3. BASELINE DATA, NEUROIMAGING, NEURODEVELOPMENTAL FOLLOW-UP

a. Baseline Data: Perinatal, demographic and in-hospital variables

i. INTRODUCTION AND FEASIBILITY: This secondary protocol will not require substantial data collection in addition to that already in place at participating centers; nor will it mandate patient management. The majority of data collection instruments will be those already routinely used by the NICHD Neonatal Research Network Survey of Morbidity and Mortality in VLBW Infants. These data are obtained through the use of "Generic Data Base forms" which allows for consistent accrual of demographic, perinatal and neonatal variables among this high-risk population.

ii. METHODS: Research nurses at participating centers will collect data using the standardized Generic Data Base Forms. Further information from the SUPPORT data collection instruments will allow delineation of the potential independent contribution of hypotension and hypocarbia to abnormalities on MRI. These factors are purported to be causes of cerebral hypoperfusion (42-46) leading to diffuse or focal neonatal brain injury. Additional data regarding respiratory status will also be collected through SUPPORT data forms.

b) Neuroimaging studies

i. INTRODUCTION AND FEASIBILITY: Changes in the approach to neuroimaging will be required for implementation of this research protocol at participating centers. The extent of the changes will depend upon the procedures already in place at each individual center

CRANIAL US: The most recent results (November 2004) of the Preterm Infant Neuroimaging Questionnaire indicate that all Network centers routinely obtain cranial US at 4-14 days among infants <28 weeks EGA. Therefore, **no additional imaging should be required to obtain "early" cranial US in any center. In addition, early US is required by SUPPORT.** A few centers do not routinely perform cranial US during the 35-42 week window; these include the two centers that currently use MRI as the routine near-term neuroimaging study, and two centers that perform near-term US only if abnormalities are noted on early US. Therefore, **additional imaging would be**

required to obtain "late" cranial US in some centers. Additional costs would also be incurred for coordinator time (tracking, gathering, sending neuroimaging studies) and central reading.

BRAIN MRI: The most recent results (November 2004) of the Preterm Infant Neuroimaging Questionnaire reveal that two Network sites currently use brain MRI as the routine near-term VLBW imaging modality, with one additional site possibly planning to implement routine MRI, and a few other sites considering a change to routine brain MRI at near-term. **For those sites utilizing MRI as the routine near-term neuroimaging modality, only one additional study, a cranial US at 35-42 weeks, would be required. For sites not performing MRI, of course, an MRI at 35-42 weeks would be required.**

ii. METHODS:

Cranial ultrasound: Cranial ultrasounds will be obtained according to standard imaging requirements (Appendix A). "Early" cranial ultrasound will be obtained at 4-14 days of age. If more than one cranial ultrasound is obtained during that time period, the "worst" ultrasound will be used – if multiple US have similar results, the US obtained closest to 14 days will be used. "Late" cranial ultrasound will be obtained at 35-42 weeks PMA. Ultrasounds will be clinically evaluated at each Network center, but central readers will formally interpret ultrasounds (see Appendix B). Cranial US studies will be sent to RTI in the form of CD (preferable) or film. Central readers will be masked to unique patient identifiers, clinical history, SUPPORT treatment arm, and Network center clinical radiologists' interpretations.

Each participating center is expected to counsel families with regard to US findings on local (center-based) clinical interpretation.

Brain MRI: A brain MRI will be obtained at 35-42 weeks PMA, and within 7 days of the "late cranial ultrasound" according to imaging requirements (Appendix A). MRIs can be clinically evaluated at each Network center, but central reader(s) will formally interpret MRIs (see Appendix B). Brain MRI studies will be sent to RTI after digital transfer to CD. Central MRI readers will include Patrick Barnes, M.D., and others as suggested by the Steering Committee. Central readers will be masked to unique patient identifiers, clinical history, SUPPORT treatment arm, and Network center clinical radiologists' interpretations.

Each participating center is expected to counsel families with regard to MRI findings on local (center-based) neuroradiologist's interpretation.

Sedation issues: MRI studies are performed without sedation at Stanford University. Patients are imaged following a feeding, ear coverings (MiniMuffs, Natus) are used to reduce the noise and patients are bundled to preserve warmth, maintain sleep and reduce patient motion. Of the 14 sites that responded to an earlier NICHD Neonatal Research Network Brain Imaging Survey, five indicated that they use sedation for MRI. Another six sites indicated that sedation is used if clinically necessary. One site responded that sedation is not used. Responses from two centers were not clear. At Stanford, the approach of "feeding and swaddling" has yielded successful conventional MRI imaging with excellent quality in most cases. Sedation, if needed,

would clearly increase the likelihood of obtaining a high quality scan. Network centers in which sedation is standard of care, and MRI is routinely performed, should certainly be able to continue their current approach. Although several of the sites have already indicated that sedation is used routinely, it is appreciated that the use of sedation in the context of a research protocol may make IRB approval more difficult. One possible solution for centers with such challenges would be to present two consent forms: the first for participation in the study itself, indicating that "feeding and swaddling" methods would be tried; the second, for consent to use sedation if this conservative approach were not successful, or if it is considered medically inadvisable to implement the "feeding and swaddling" approach (i.e., severe reflux). Clearly there are differing approaches to sedation for MRI studies, and differing protocols in place at each center – thus, the issue of sedation must be left to the individual investigators at each Network site.

c) Neurodevelopmental Follow-up

i. INTRODUCTION AND FEASIBILITY: Neurodevelopmental follow-up for ELBW infants is already a focused objective within the NICHD Neonatal Research Network; all Network centers have complete neurodevelopmental assessment teams and patient tracking infrastructure in place. Neurodevelopmental follow-up is required by the SUPPORT protocol.

ii. METHODS: Follow-up visit will be conducted at 18-22 months corrected age as described in the "NICHD Neonatal Research Network ELBW Follow-Up Study Manual of Operations" and in previous publications (14).

4. STATISTICAL CONSIDERATIONS

Outcomes:

Primary outcomes include

- Death/Grade 3/4 IVH on 4-14 day cranial US
- Death/Grade 3/4 IVH on 35-42 week cranial US
- Death/PVL on 35-42 week cranial US
- Death/abnormal MRI at 35-42 weeks

Secondary outcomes include

- Moderate to severe cerebral palsy
- BSID MDI<70
- BSID PDI<70
- Neurodevelopmental impairment (NDI) defined as any of the following: deafness, blindness, moderate-severe cerebral palsy, or BSID II MDI or PDI score <70.

Bivariate analyses: Analyses of frequency of primary outcomes with respect to SUPPORT treatment groups will be undertaken. Comparisons will be made between ventilation strategy groups (Early CPAP and Control groups) within each randomized oxygenation group, and between oxygenation strategy groups (Low and High SpO2) within each randomized ventilation group. Continuous measures will be compared using the Student t-test and ANOVA where appropriate, and Chi-square analysis will be used

to compare categorical data. These analyses would also adjust for the clustering effect introduced by randomizing by week of study.

Sample size and power issues:
Overall GDB and follow-up patient numbers: For year 2003, 1468 infants 24+0 to 27+6 weeks EGA were enrolled in GDB. Of those, 1249 survived to >7 days and 1209 survived to >=14 days. 1027 patients survived to hospital discharge. In year 2003, a total of 725 former 24+0 to 27+6 week EGA patients completed neurodevelopmental assessment at 18-22 months corrected age.
Frequency of neuroimaging outcomes:
Ultrasound: For year 2003, among infants 24+0 to 27+6 weeks EGA surviving to >=14 days, the frequency of Grade 3/4 IVH on cranial US was 20.3%; for those surviving to discharge it was 18.6%. The frequency of PVL among those surviving to discharge was 3.9%.
MRI: "Abnormal" MRI results among preterm infants at near term are much more difficult to quantify due both to a paucity of available data in the literature, and disparate methods for reporting and scoring "abnormalities". Two recent studies have attempted to estimate the frequency of white matter signal abnormality, as well as other abnormal findings. Inder and colleagues (47) reported on findings of brain MRI performed at term equivalent age in 100 infants of 23-32 weeks EGA. Only 36/100 were considered to have no white matter signal abnormality, whereas 16/100 had extensive severe white matter signal abnormality. Cortical gray matter abnormalities were rare, with 96/100 patients categorized as normal. Lateral ventricle size was normal in only 40/100 (60% abnormal). Miller, et. al. (48) reported on MRI findings of 32 consecutive preterm infants, but imaging was performed at earlier postconceptual ages. In addition, Maalouf (27) found that 12/19 (63%) preterm infants studied by MRI at 38-44 weeks PCA had abnormal white matter signal, but of those only 7 were moderately to severely abnormal (37%). Childs (30) found 29 of 105 preterm infants (<37 weeks) had abnormal periventricular white matter on MRI, and an additional 5 infants with other abnormalities (32% abnormal). However, the age at the time of MRI ranged from 1-42 days, PCA at time of scan was not reported, and the average gestational age in that study was greater than that of the source population for SUPPORT. Counsell, et. al. found that, among preterm infants at near term, 34 of 50 had "overt" white matter abnormality or diffuse excessive high signal intensity white matter abnormalities (68% abnormal) (39). In summary, the frequency of "abnormal" brain MRI in preterm infants ranges from 32-68%. One projected benefit from this proposed secondary study, in fact, would be to better understand the frequency and type of MRI abnormalities in a large premature group. For the purposes of sample size and power calculations for this proposal, a conservative estimate of 40% white matter abnormality by MRI at 35-42 weeks will be used.

Thus, the following are the estimated frequencies for four major outcomes examined in this proposal:

I) Death/Grade 3/4 IVH (14 day)	34.2%
II) Death/Grade 3/4 IVH (at d/c, an estimate of 35-42 weeks)	42.9%
III) Death/PVL (at d/c, an estimate of 35-42 weeks)	32.8%

IV) Death/MRI abnormality 58%

The revised projected sample size required for SUPPORT is 1310 patients (or 328 patients per each of 4 treatment groups). It is unlikely that all centers could participate in this secondary.

The increased relative risks detectable with corresponding sample size per group were calculated using alpha = 0.05, power = 0.8 are shown below. "Group" sample size refers to the number of patients in each unique randomized respiratory strategy, such that bivariate comparisons will be made between ventilation strategy groups (Early CPAP vs. Control ventilation groups) within each randomized oxygenation strategy, and between oxygenation strategy groups (Low vs. High SpO2) within each randomized ventilation strategy.

For Death/IVH 3_4 at 14 days, using an expected baseline prevalence of 34.2%

RR	sample size per group
1.3	356
1.4	203
1.5	132
1.6	93
1.7	69
1.8	53

For Death/IVH 3_4 at 35-42 weeks, using an expected baseline prevalence of 42.9%:

RR	sample size per group
1.2	532
1.3	237
1.4	134
1.5	85
1.6	59

For Death/PVL at 35-42 weeks, using an expected baseline prevalence of 32.8%:

RR	sample size per group
1.3	381
1.4	218
1.5	142
1.6	100
1.7	74
1.8	57

For Death/MRI abnormality at 35-42 weeks, using an expected baseline prevalence of 58%:

RR	sample size per group
1.2	270
1.3	116
1.4	62
1.5	38

1.6 25

The detectable relative risks were also calculated for an alpha of 0.01 to conservatively adjust for the four primary outcomes. Thus,

For Death/IVH 3_4 at 14 days, using an expected baseline prevalence of 34.2%:

RR	sample size per group
1.4	303
1.5	196
1.6	138
1.7	102
1.8	79
1.9	62
2.0	51

For Death/IVH 3_4 at 35-42 weeks, using an expected baseline prevalence of 42.9%:

RR	sample size per group
1.3	354
1.4	199
1.5	127
1.6	88
1.7	64
1.8	48

For Death/PVL at 35-42 weeks, using an expected baseline prevalence of 32.8%:

RR	sample size per group
1.4	325
1.5	211
1.6	148
1.7	110
1.8	85
1.9	68
2.0	55

For Death/MRI abnormality at 35-42 weeks, using an expected baseline prevalence of 58%:

RR	sample size per group
1.2	402
1.3	172
1.4	93
1.5	56
1.6	36

Regression Analyses: In addition to bivariate analyses, regression analyses will be undertaken to attempt to adjust for confounding variables in comparisons of treatment groups with respect to neuroimaging findings.The independent association of ventilation strategy will be determined for each neuroimaging outcome (Grade 3/4 IVH at 4-14

days, 35-42 weeks, PVL at 35-42 weeks, MRI abnormality), adjusting for gestational age, weight, and oxygenation strategy. Similarly, the independent association of oxygenation strategy will be determined for each neuroimaging outcome (Grade 3/4 IVH at 4-14 days, 35-42 weeks, PVL at 35-42 weeks, MRI abnormality), adjusting for gestational age, weight, and ventilation strategy.

Neurodevelopmental Outcomes Logistic Regression Models: Models will be developed to include perinatal, demographic, neonatal and socioeconomic factors pertinent to neurodevelopmental outcome as demonstrated in previous reports (14,15) and the univariate and multivariate analyses carried out. Confounding factors to be examined when building models will include, but may not be limited to: Network center, cesarean section, race, EGA, birth weight, PDA, intubated in DR, any sepsis, NEC, BPD, ROP stage>=3 with plus, antenatal steroids, postnatal steroids, indomethacin prophylaxis, education<HS in primary caregiver surfactant, primary language not English, living with the mother, discharged on oxygen, Medicaid insurance. Neuroimaging study results (cranial US at 4-14 days, cranial US at 35-42 weeks PMA, and brain MRI at 35-42 weeks) will be added to the model individually and in combination, to determine the adjusted risk for adverse outcome that each imparts, and to ascertain if any two abnormal studies (i.e., early cranial US and MRI, or early and late US) are materially more predictive of neurodevelopmental impairment than any single abnormal study. Ventilatory strategy and oxygen saturation strategy will also be available as crucial neonatal factors that may impact on outcome.

Predictive modeling of outcome: Challenges to the development of a predictive model include the need for both a "model development" data set and a "model validation" data set. Possible solutions to this challenge include splitting the proposed study data set (70/30), thus creating a development and validation set; or by employing a cross-validation or "boot-strapping" techniques (49). Further analysis will be required to determine the best strategy for predictive modeling in the proposed study. Model calibration and goodness-of-fit will be evaluated by Hosmer-Lemeshow statistic, and predictive ability by AUC of ROC curves.

APPENDICES

Appendix A: Neuroimaging requirements

Cranial ultrasound: The number of planes and images outlined below are considered to be the "standard" procedure for neonatal cranial US scanning through the anterior fontanelle. It is understood that additional planes and images (i.e., posterior fontanelle views, mastoid views) are obtained in some centers:

- Coronal views: The base of the skull should be symmetric on coronal scans.
    - Six views:
        - Orbital roofs (includes intracerebral fissure, frontal cortex and gyri)
        - Pentagon (includes anterior horns of lateral ventricles, tips of temporal lobes, basal ganglia)
        - Third ventricle
        - Fourth ventricle
        - Lateral ventricle choroid plexus

  - Posterior (includes occipital horns of lateral ventricles, parietal and occipital cortex)
- Sagittal views
  - Midline
  - Right lateral ventricle
  - Right lateral parasagittal
  - Left lateral ventricle
  - Left lateral parasagittal

MRI: Items 1-7 will be mandatory for this protocol. If a Network center is also obtaining diffusion sequences (Item 8), tensor DTI with 6 directions may be performed, but 32 directions will be preferred.

1) Sag. T1 CSE: TR 500 / TE 20 / Slice 3 / gap 1 / FOV 20 / matrix 256 x 192 / NEX 1 (for localizer and corpus callosum).

2) Axial T1 CSE: 500 / 20 / 4 / 0 / 20 / 256 x 192 / 1

3) Axial T2 FSE: 3350/ 99 / 4 / 0 / 20 / 256x192 / 2 / ETL 8

4) Axial FLAIR: 9000 / 103 / 4 / 0 / 20 / 256x192 / 1-2 / TI 2200

5) Axial GRE: 500 / 15-30 / 4 / 0 / 20 / 256x192 / 1 / Flip angle 15

6) Axial or Coronal 3D SPGR: 24 / min. 8 / 1.5 / 0 / 20-22 (phase FOV 0.75) / 256x224 / 0.75 / FA 30

7) DWI: 4000 / min. 71/4/0/20/1128x128/1/b-value 1000/# directions - 6.

[8) Tensor DTI: 4000 / min. 71 / 4 / 0 / 20 / 128x128 / 1 / B-value 1000 / # directions – 32]

Appendix B: Neuroimaging interpretation – <u>CENTRAL reading</u>

Cranial ultrasound CENTRAL reading interpretation will focus on the following for both "early" and "late" studies:
<u>Echodensities</u>:
If present, laterality and locations will be queried:
Subependymal
Periventricular
Frontal, temporal, parietal, occipital
Intracerebral
Frontal, temporal, parietal, occipital, thalamus, posterior fossa
Intraventricular (see "Hemorrhage Classification" below)
Other

Echolucencies
If present, laterality and locations will be queried:
- Subependymal
- Periventricular
  - Frontal, temporal, parietal, occipital
- Intraparenchymal
  - Frontal, temporal, parietal, occipital, thalamus, posterior fossa
- Other parenchymal
  - Calcification, cerebral edema, cortical atrophy, extra-axial fluid (volume will be specified), infarct, LS branching, other

Ventricles
Choroid abnormalities:
- Cyst
- Other (including hemorrhage)

Ventricle size abnormalities:
- Mild increase, moderate increase, marked increase

Shunt present

Hemorrhage Classification
- Grade I, Grade II, Grade III, Grade IV, Other

Structural Abnormalities
- Specify (comment)

MRI CENTRAL reading interpretation will focus on **(SEE *DRAFT* MRI SCORING FORM AND KEY for central readers):**
Signal Abnormalities – If present, size, number of lesions, sidedness, and location (frontal, temporal, parietal, occipital, cerebellar, periventricular, cortical, subcortical, basal ganglia/thalamus, brain stem) lwill be queried.
- White matter
  - Cystic (low signal T1, high signal T2, low signal FLAIR)
  - Non-cystic (high or low T1, high T2, high FLAIR)
  - Hemorrhagic or mineralization (low T1 +/- low GRE, low T2)
  - Diffuse excessive high signal intensity (DEHSI)
- Gray Matter
  - Cystic
  - Non-cystic

Maturation and Development
- White matter
  - *Markers of myelination*: We will use a scoring system modified from McArdle (50), Huppi (51), Childs (52), Counsell (53). We will indicate myelination markers for right and left sides using both T1 and T2-weighted imaging: W0 = extremely immature; W1 = <=30 weeks; W2=36 weeks; W3 = 37-42 weeks
  - *Corpus callosum thinning*: none, mild-moderate, marked
  - *Lateral Ventricle size enlargement*: none, mild-mod, marked

Gray matter

Cortical maturation markers: We will use a scoring system modified from Chi (54), McArdle (50), Inder (47), and Childs (52). G0=immature (<34 weeks); G1=34-36 weeks; G2=36-38 weeks; G3=40 weeks.

Subarachnoid space enlargement: normal (<4 mm), mild-mod (4-6 mm), marked (>6 mm)

Ventricles

Choroid cysts
Choroid hemorrhage
Intraventricular hemorrhage
Shunt present?

Structural abnormalities

Comments

Human Subjects

1. Risks to the subjects:

a) Human Subjects Involvement and Characteristics: Infants enrolled in the NICHD Neonatal Research Network SUPPORT trial will be recruited. Inclusion and Exclusion criteria have been defined as stated in the Research Plan. The final population will be dependent upon the number of sites within the Network that participate in this study. Both male and female infants will be enrolled. We expect the study population to be representative of the racial background and gender distribution of the Neonatal Research Network. In 2001, 49% male and 51% female patients constituted the ELBW population of the Neonatal Research Network, of which 43% were black, 38% were white, 15% were hispanic, and 3% were other races.

b) Sources of Materials: Sources of research material will consist of perinatal, demographic and neonatal data collected by research personnel as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality Among VLBW Infants (401-1500 g), and through the data collection mechanisms associated with the SUPPORT trial. Additional data will be obtained through evaluation of brain MRI images by a central reader masked to all patient identifiers and patient outcomes. Data forms will be created, completed by the central MRI reader, and submitted to Research Triangle Institute per protocol. Neurodevelopmental outcome data will be obtained from the NICHD Neonatal Research Network Follow-up Study of ELBW Infants, and per SUPPORT specifications.

c) Potential Risks: The risks and discomforts of participation are minimal as the study relies primarily on data collected for ongoing studies already in progress, and uses non-invasive techniques. Cranial US is performed routinely in all NICU's in the NICHD Neonatal Research Network, is considered standard of care, and techniques would not be altered by this study. Brain MRI at 35-42 weeks postmenstrual age is already routine in several Network centers. Sedation will not be used routinely, although may be used particularly in centers that already do use sedation. Temporary minor skin irritation from tape used to apply MRI-compatible monitoring electrodes may occur, but this risk is unlikely. Temporary transport of a patient to a radiology suite for MRI may also represent a possible risk; however, only those patients considered stable for transport will undergo imaging, and a 7- week window of opportunity for MRI is built into

the proposed study. The alternative to obtaining a brain MRI as part of the proposed study is non-enrollment.

2. Adequacy of Protection Against Risks:
a) Recruitment and Informed Consent :
Screening: The individual center will be responsible for devising a screening strategy to identify all potential participants using the study inclusion and exclusion criteria. Screening, identification and informed consent procedures should be completed by 14 days of age as "early cranial US" must be performed by this time.
Informed consent: Each participating center will follow procedures for developing informed consents as set out by their Institutional Review Board (IRB). The parents of all infants enrolled in SUPPORT will be approached to participate in this secondary study, and informed consent must be obtained by the individual center. Informed consent will be obtained by the Principal Investigator or his/her designee.
Eligible infants not enrolled: The reasons for non-enrollment of eligible infants will be documented. Short- and long-term outcomes of eligible infants not enrolled in this study will be documented as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality in Very Low Birth Weight (VLBW) Infants (Generic Data Base (GDB)) and, if enrolled, as part of the ongoing NICHD Neonatal Research Network ELBW Neurodevelopmental Follow-Up Study.
No MRI obtained for enrolled infants: The objective of the proposed study requires acquisition of cranial US and MRI at 35-42 weeks PMA; if the patient is deemed medically unstable during the entire 35-42 week PMA period, an MRI will not be obtained during that period, but MRI could then be delayed. Other reasons for inability to obtain the MRI will also be documented.
b) Protection against risk: Every effort will be made to protect study patients from potential risks of participation. Stability of study patients for transport to a radiology suite for brain MRI will be assessed by the attending neonatologist at each participating site. Any adverse events with regard to obtaining neuroimaging studies among enrolled patients will be documented and submitted to NICHD, the data center, and the local IRB. The NICHD Neonatal Research Network has an independent Data Safety Monitoring Committee (DSMC), which would provide continuous oversight of patient safety and risk factors for the duration of the study. The DSMC will review the study on at least an annual basis.

3. Potential Benefits of the proposed research to the subjects and others: The potential benefits of participation to an individual patient include identification of structural anomalies by MRI that would not have been identifiable by ultrasound. This may allow for early, targeted intervention for the individual patient that otherwise would not have been undertaken. Other potential benefits would be to future extremely preterm patients after results of this prospective study are known (see below).

4. Importance of the knowledge to be gained:
Provide a thorough neuroimaging monitoring arm for SUPPORT: Although cranial US is a standard diagnostic procedure in the NRN, the proposed study would provide a framework for specifically timed cranial US studies (early and late). In addition, subtle

but potentially extremely important findings consistent with brain injury would be detectable by MRI.

Counseling, follow-up: Detection of an injury pattern which is consistent with later neurodevelopmental delay will be useful for counseling and targeted, early follow-up. Identifying such a tool would provide a link to later research in early intervention.

Clarify the pathogenesis of injury leading to neurodevelopmental impairment: Further delineation of pathophysiologic correlates of later outcome could possibly be linked with perinatal and neonatal factors, which would 1) focus future research and intervention on clinical events associated with the pathophysiologic hallmark, 2) provide important data leading to further study of the pathogenesis and timing of injury, and 3) assess neuroanatomic localization of subtle injury associated with later neuromotor abnormalities.

Contribution to the literature with respect to diagnostic strategies for the extremely preterm population: Previous neuroimaging practice parameters have concluded that insufficient evidence exists to recommend advanced neuroimaging for premature infants for prediction of neurodevelopmental outcomes. The proposed study would address this significant gap in the collective literature.

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Is your child participating in any other research studies? _____ yes _____ no

Informed Consent

Your child is invited to participate in a research study to find out more about treatment with CPAP (positive air pressure to help keep the lungs inflated) and learn the appropriate levels of oxygen in the blood in premature infants. You are being asked to allow your child to be in the study because there is a possibility that (s)he will be born 12-16 weeks early (at 24 to 28 weeks of pregnancy).

The study, funded by the National Institutes of Health, is being conducted at Stanford and other medical centers across the country to 1) compare infants who receive delivery room CPAP and who have specific guidelines for having a breathing tube placed with infants who have a breathing tube placed and surfactant (a liquid which helps babies with immature lungs breath easier by helping keep their lungs from collapsing) given in the delivery room and 2) compare low range (85-89%) oxygen levels (saturation) with high range (91-95%) levels to determine if a lower range results in decreased ROP (Retinopathy of Prematurity, an eye disease that may result in impairment of vision or even blindness, which may be caused by excessive levels of oxygen.) Nationwide, a total of 1300 patients are expected to enroll in this study over about two years and we expect about 25 of those infants will be from Stanford. Children who are enrolled in the study will be involved for about two years.

If you decide to allow your child to be in this study, a few minutes before your child is born, (s)he will be randomly assigned, like the flip of a coin, to one of two lung treatment strategies. The treatments are as follows: 1) CPAP in the delivery room immediately after birth and continuing in the intensive care nursery (NICU), or 2) placement of a tube in the windpipe in the delivery room followed by surfactant administration and ventilation (breathing for the baby using a machine). Infants randomized to the CPAP group may, at some point in their care, require a windpipe tube and a breathing machine. If the attending physician deems this necessary, participation in the study will not affect this decision. Study guidelines for lung treatments of infants in both groups will be followed for two weeks.

In addition to being randomly assigned to one of the two groups described above, your baby will be randomly assigned to having a blood oxygen monitor (oximeter) which reads slightly high or one that reads slightly low. The oximeters used in this study are FDA approved device which have been modified for research purposes. This modification makes the monitors show an oxygen saturation value which is either a little higher or a little lower than the true oxygen saturation when values are in the normal range (between 85 and 95%). Outside those ranges, the oximeter works the same as a standard oximeter. This will allow the study to keep the saturations at the high and low ends of the normal range and still protect the study infants from saturations that may be too low or too high. The doctors and nurses taking care of your infant

will not know if (s)he is in the high or low saturation group. This is to help assure that all patients are cared for in the same way. Your child will be on a study oximeter until about four weeks before the original "due date". At that time, the oximeter will be changed to a standard one for the remainder of his/her hospital stay.

Your infant will be assigned to one of the four groups shown below. Neither your or the doctors taking care of your infant will be able to choose which group your infant is assigned to. The assignments will be made randomly, like the flip of a coin.

CPAP Higher oxygen saturation	CPAP Lower oxygen saturation
Breathing tube + breathing machine Higher oxygen saturation	Breathing tube + breathing machine Lower oxygen saturation

Part of your child's regular care during the first few weeks after birth will include one or more head ultrasounds. In addition, within about four weeks of your child's planned due-date, your child will have an MRI of the brain. The ultrasounds and MRI studies create pictures (images) of the brain which are used to look for brain injury. Children who participate in this study will have an ultrasound at the time the MRI is done so the doctors conducting the project can compare the findings and determine if one way of imaging gives more useful information than the other.

Other aspects of your infant's care will be the standard treatments for premature babies in the Stanford NICU. All children who participate in the project will return to the Development and Behavior Unit at regular intervals during the first two years as part of their routine care. When the children enrolled in this study return for their 18-22 month old assessments of growth, development, and coordinated movement skills, the study will collect that outcome information.

Participation in this study may involve some added risks or discomforts. Because all of the treatments proposed in this study are within standard of care, there is no predictable increase in risk for your baby. There is no known risk or discomfort associated with the extra head ultrasound. Some unknown risks may be learned during the study. You will be told of any new

information that is learned which may affect your child's condition or influence your willingness to have him/her continue participation in this study. The only other risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential.

There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen near discharge) and/or a decrease in the need for eye surgery as a result of exposure to oxygen. Because we do not know in advance the actual strategies chosen for your child, or which of the treatment strategies is the most effective, it is also possible that your baby will receive no direct benefit. The knowledge learned from this study may help us treat babies in the future. However, each of the 4 possible combinations of treatments is considered by some NICUs to represent their desired approach.

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOUR CHILD WILL RECEIVE ANY BENEFIT FROM THIS STUDY.

The alternative to having your child participate in this project is not to participate. You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you choose not to have your child participate, he/she will receive the standard care for premature infants including oxygen, and help to breath as needed.

Any data that may be published in scientific journals or presented at scientific or medical meetings will not reveal the identity of your child. Patient information may be provided to Federal and regulatory agencies as required. The Food and Drug Administration, for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

Your child's participation in this study is entirely voluntary.
Your decision whether or not to allow your child to participate will not prejudice your child or his/her medical care. If you wish to allow your child to participate in this study, you must sign this consent form and the authorization form. If you decide to let your child participate, your are free to withdraw your consent, including your authorization regarding the use and disclosure of your child's health information, and to discontinue participation at any time without prejudice to your child or effect on your child's medical care. If you decide to terminate your child's participation in this study, you should notify Dr Stevenson or Dr Van Meurs at (650) 723 5711.

The early part of the project will last until the end of your child's hospital stay. In order to successfully evaluate the approaches to lung treatment and oxygen used in this study, Dr. Stevenson and his associates will want to collect information about your baby's general health, and any hospitalizations during the first two years of life. By agreeing to participate in this study, you give consent for the release of medical records from other medical facilities and providers of medical care to Dr. David Stevenson and his associates. Follow up at 18-22 months is essential for this study. Families who participate in this project are agreeing to remain in contact with the investigators and to return to the Mary L. Johnson Development and Behavior Unit at Packard Children's Hospital with their child when (s)he is 18 months of age.

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While participating in this study, your child should not take part in any other research project without approval from all of the investigators. This is to protect your child from possible injury arising from such things as extra blood drawing, extra x-rays, interaction of research drugs, or similar hazards.

No payment will be provided for this project. You or your insurance company will be responsible for the costs incurred in your child's care because that care will not be different from what is usually provided by the nursery staff. The study will pay for the extra ultrasound obtained around the due-date. You or your insurance company will not incur additional charges by having the study ultrasound. The National Institutes of Health and National Institute of Child Health and Human Development are providing financial support and/or materials for this study.

At the discretion of the protocol director subjects may be taken out of this study due to unanticipated circumstances. Examples of reasons for taking a participant out of the study include: the investigator deciding that continued participation could be harmful to your child, the study being canceled, some other administrative reason.

If you think your child has experienced a research-related injury, call Dr Stevenson or Dr Van Meurs at 650 723 5711.

If you have any questions about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the protocol directors. You may contact Dr Stevenson or Dr Van Meurs at 650 723 5711. If you have any additional questions later, Dr Stevenson and Dr Van Meurs at (650) 723 5711 will be happy to answer them.

All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, your child might develop medical complications from participating in this study. If such complications arise, the investigators will assist you in obtaining appropriate medical treatment but this study does not provide financial assistance for additional medical or other costs. Additionally, Stanford is not responsible for research and medical care by other institutions or personnel participating in this study. You do not waive any liability rights for personal injury by signing this form. For further information, please call (650) 723-5244 or write the Administrative Panel on Human Subjects in Medical Research, Administrative Panels Office, Stanford University, Stanford, CA 94305-5401. In addition, if you are not satisfied with the manner in which this study is being conducted or if you have any questions concerning your child's rights as a study participant, please contact the Human Subject Office at the same address and telephone number.

As a human subject your child has the following rights. These rights include but are not limited to the subject's right to:

- be informed of the nature and purpose of the experiment;

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- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if
- applicable;
- be given a disclosure of any appropriate alternatives, drugs, or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise;
- be given an opportunity to ask any questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form, and be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, coercion or undue influence on the subject's decision.

YOUR SIGNATURE INDICATES THAT YOU HAVE READ AND UNDERSTAND THE ABOVE INFORMATION, THAT YOU HAVE DISCUSSED THIS STUDY WITH THE PERSON OBTAINING CONSENT, THAT YOU HAVE DECIDED TO PARTICIPATE BASED ON THE INFORMATION PROVIDED, AND THAT A COPY OF THIS FORM HAS BEEN GIVEN TO YOU.

_____ _____
Signature of Legally Authorized Representative Date

_____
Description of Representative's Authority to Act for Subject

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied-that the participant has been provided with the Experimental Subject's Bill of Rights, if appropriate, that I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

_____ _____
Signature of Person Obtaining Consent Date

Approval Date: February 22, 2005 Expiration Date : February 21, 2006

Cooperative Multicenter Network of Neonatal Intensive Care Units:
The Surfactant Positive Airway Pressure and Pulse Oximetry Trial
in Extremely Low Birth Weight Infants
Director: David K Stevenson, M.D.

Authorization To UseYour Child's Health Information For Research Purposes

Because information about your child and his/her health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your child's health information will be used or disclosed in the study. Your child's information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my child's health information be utilized in the study?

The study is designed to find out more about the best way to help the breathing of babies who are born very early and to learn the appropriate levels of oxygen in their blood. Your child's health information will be used to compare the characteristics, such as birth weight, of the children in the four study groups, compare the amount of breathing help they need, oxygen levels, results of eye exams, and need for oxygen when they are close to their due dates. This information will be sent to the study data center and the sponsor (National Institutes of Health). The information will have your child's study number on it, not his/her name. The results of the study will be published in a scientific or medical journal but the identities of children who were in the study will not be disclosed.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, your child will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw my child from the research later?

If you decide to allow your child to participate, you are free to withdraw your authorization regarding the use and disclosure of your child's health information (and to discontinue any other participation in the study) at any time. After any

revocation, your child's health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to

revoke your authorization for the research use or disclosure of your child's health information in this study, you must write to: Dr David K Stevenson or Dr Krisa Van Meurs, Division of Neonatology, 750 Welch Road, Palo Alto, CA 94304.

What Personal Information Will Be Used or Disclosed?

Your child's health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, perinatal and birth records, physical examinations, laboratory records, respiratory records, nursing records, vital signs, x-rays, ultrasounds, MRIs, medication records, psychometric parameters, visual function and acuity, and auditory function may be used or disclosed in connection with this research study.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your child's health information in connection with this research study:

- The Protocol Director, David Stevenson, MD
- The Assistant Protocol Director, Krisa Van Meurs, MD
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- The research coordinator, nurses, research assistants and data clerk

Who May Receive / Use the Information?

The parties listed in the preceding paragraph may disclose your child's health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- The National Institutes of Health

- Research Triangle Institute (data management center)

Your child's information may be redisclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your child's health information will continue until December 31, 2100.

Cooperative Multicenter Network of Neonatal Intensive Care Units:
The Surfactant Positive Airway Pressure and Pulse Oximetry Trial
in Extremely Low Birth Weight Infants
Director: David K Stevenson, M.D.

Will access to my child's medical record be limited during the study?

To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make medical or billing decision about your child (e.g., if included in your official medical record).

_____ _____

Signature of Legally Authorized Representative Date

_____

Description of Representative's Authority to Act for Subject

Cooperative Multicenter Network of Neonatal Intensive Care Units:
Neuroimaging and Neurodevelopmental Outcome: A Secondary Study to SUPPORT

Is your child participating in any other research studies? _____ yes _____ no

Informed Consent

Your child is invited to participate in a study of ultrasound and MRI imaging (pictures) of the brain, which are used to look for brain injury. This research study is designed to compare brain imaging by ultrasound and magnetic resonance imaging (MRI), done around the time when a baby would normally is born, to determine if one method of imaging gives more useful information than the other. Your child is eligible to be in this study because he/she is enrolled in the Surfactant Positive Airway Pressure and Pulse Oximetry Trail (SUPPORT).

The study, funded by the National Institutes of Health, is being conducted at Stanford and other medical centers across the country. Nationwide, up to 1300 patients will be eligible to enroll in this part of the study over about two years. We expect that about 25 of those infants will be from Stanford. Children who are enrolled in the study will be involved for about two years.

Part of your child's regular care during the first few months after birth will include one or more head ultrasounds to check for brain injury, including at about the time he/she would normally have been born. If you decide to allow your child to be in this study, he/she will also have a brain MRI within about a month of his/her intended due date. MRI is a method of making pictures of both normal and abnormal changes within the body. It is based on the relationship between atoms within the body when placed inside a large magnet. MRI uses a magnetic field to make images of the body interior. The scanning procedure is very much like an X-ray CT scan. Your child will be placed on a long narrow couch for 20 to 30 minutes while the machine gathers data. During this time, your child will not be exposed to radiation or X-rays but, rather, a strong magnetic field and radiofrequency magnetic fields. Your child will not feel either. Your child will, however, hear repetitive tapping noises that arise from the gradient coils of the MRI machine. We will provide earmuffs that your child will wear. Generally, infants who are fed, wrapped in warm blankets, and have earmuffs in place, sleep through MRIs. There are no known risks associated with this procedure. The exception is if your child has a certain type of metallic clip in the body (such as an aneurysm clip in his/her brain), any history of head or eye injury involving metal fragments, some type of implanted electrical device (such as a cardiac pacemaker), or if your child has severe heart disease (including susceptibility to arrhythmias), your child should not have an MRI except under specified indications with proper precautions. There is a possibility that your child will experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful.

The magnetic fields do not cause harmful effects at the levels used in the MRI machine. National and local guidelines have been developed for these machines, and these recommendations will be followed. However, because the MR scanner uses a very strong magnet that will attract metal, all metallic objects must be removed from your child's person before approaching the scanner

Other aspects of your infant's care will be the standard treatments for premature babies in the Stanford NICU. All children who participate in the project will return to the Development and Behavior Unit at regular intervals during the first two years as part of their routine care. When

the children enrolled in this study return for their 18-22 month old assessments of growth, development, and coordinated movement skills, the study will collect that outcome information.

All of the imaging proposed in this study is within standard of care, there is no predictable increase in risk for your baby. Some unknown risks may be learned during the study. You will be told of any new information that is learned which may affect your child's condition or influence your willingness to have him/her continue participation in this study. The only other risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential.

There may be benefits to your child directly, including detection of brain injury which will allow for earlier intervention than would normally occur. It is also possible that your baby will receive no direct benefit. The knowledge learned from this study may help us treat babies in the future.

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOUR CHILD WILL RECEIVE ANY BENEFIT FROM THIS STUDY.

The alternative to having your child participate in this project is not to participate. You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you choose not to have your child participate, he/she will receive the standard care for premature infants including oxygen, and help to breath as needed.

Any data that may be published in scientific journals or presented at scientific or medical meetings will not reveal the identity of your child. Patient information may be provided to Federal and regulatory agencies as required. The Food and Drug Administration, for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

Your child's participation in this study is entirely voluntary.
Your decision whether or not to allow your child to participate will not prejudice your child or his/her medical care. If you wish to allow your child to participate in this study, you must sign this consent form and the authorization form. If you decide to let your child participate, your are free to withdraw your consent, including your authorization regarding the use and disclosure of your child's health information, and to discontinue participation at any time without prejudice to your child or effect on your child's medical care. If you decide to terminate your child's participation in this study, you should notify Dr Hintz, Dr Van Meurs, or Dr Stevenson at (650) 723 5711.

The early part of the project will last until the end of your child's hospital stay. In order to successfully evaluate the approaches to lung treatment and oxygen used in this study, Dr. Stevenson and his associates will want to collect information about your baby's general health, and any hospitalizations during the first two years of life. By agreeing to participate in this study, you give consent for the release of medical records from other medical facilities and providers of medical care to Dr. David Stevenson and his associates. Follow up at 18-22 months is essential for this study. Families who participate in this project are agreeing to remain in contact with the investigators and to return to the Mary L. Johnson Development and Behavior Unit at Packard Children's Hospital with their child when (s)he is 18 months of age.

While participating in this study, your child should not take part in any other research project without approval from all of the investigators. This is to protect your child from possible injury arising from such things as extra blood drawing, extra x-rays, interaction of research drugs, or similar hazards.

No payment will be provided for this project. The study will pay for the MRI. You and your insurance company will not incur additional charges by having the study MRI. You or your insurance company will be responsible for all other costs incurred in your child's care because that care will not be different from what is usually provided by the nursery staff. The National Institutes of Health and National Institute of Child Health and Human Development are providing financial support and/or materials for this study.

At the discretion of the protocol director subjects may be taken out of this study due to unanticipated circumstances. Examples of reasons for taking a participant out of the study include: the investigator deciding that continued participation could be harmful to your child, the study being canceled, some other administrative reason.

If you think your child has experienced a research-related injury, call Dr Hintz, Dr Van Meurs, or Dr Stevenson at 650 723 5711.

If you have any questions about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the protocol directors. You may contact Dr Hintz, Dr Van Meurs, or Dr Stevenson at 650 723 5711. If you have any additional questions later, Dr Hintz, Dr Van Meurs, or Dr Stevenson at (650) 723 5711 will be happy to answer them.

All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, your child might develop medical complications from participating in this study. If such complications arise, the investigators will assist you in obtaining appropriate medical treatment but this study does not provide financial assistance for additional medical or other costs. Additionally, Stanford is not responsible for research and medical care by other institutions or personnel participating in this study. You do not waive any liability rights for personal injury by signing this form. For further information, please call (650) 723-5244 or write the Administrative Panel on Human Subjects in Medical Research, Administrative Panels Office, Stanford University, Stanford, CA 94305-5401. In addition, if you are not satisfied with the manner in which this study is being conducted or if you have any questions concerning your child's rights as a study participant, please contact the Human Subject Office at the same address and telephone number.

As a human subject your child has the following rights. These rights include but are not limited to the subject's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if
- applicable;

- be given a disclosure of any appropriate alternatives, drugs, or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise;
- be given an opportunity to ask any questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form, and be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, coercion or undue influence on the subject's decision.

YOUR SIGNATURE INDICATES THAT YOU HAVE READ AND UNDERSTAND THE ABOVE INFORMATION, THAT YOU HAVE DISCUSSED THIS STUDY WITH THE PERSON OBTAINING CONSENT, THAT YOU HAVE DECIDED TO PARTICIPATE BASED ON THE INFORMATION PROVIDED, AND THAT A COPY OF THIS FORM HAS BEEN GIVEN TO YOU.

_____ _____

Signature of Legally Authorized Representative Date

_____

Description of Representative's Authority to Act for Subject

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied-that the participant has been provided with the Experimental Subject's Bill of Rights, if appropriate, that I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

_____ _____

Signature of Person Obtaining Consent Date

Approval Date: Expiration Date :

Authorization To UseYour Child's Health Information For Research Purposes

Because information about your child and his/her health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your child's health information will be used or disclosed in the study. Your child's information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my child's health information be utilized in the study?

The study is designed to compare ultrasound and MRI of the brain to determine if one method of imaging gives more useful information than the other. Your child's health information will be used to compare the characteristics, such as birth weight, of the children in the four study groups, compare the amount of breathing help they need, oxygen levels, results of eye exams, and need for oxygen when they are close to their due dates. This information will be sent to the study data center and the sponsor (National Institutes of Health). The information will have your child's study number on it, not his/her name. The results of the study will be published in a scientific or medical journal but the identities of children who were in the study will not be disclosed.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, your child will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw my child from the research later?

If you decide to allow your child to participate, you are free to withdraw your authorization regarding the use and disclosure of your child's health information (and to discontinue any other participation in the study) at any time. After any revocation, your child's health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your child's health

information in this study, you must write to: Dr David K Stevenson or Dr Krisa Van Meurs, Division of Neonatology, 750 Welch Road, Palo Alto, CA 94304.

What Personal Information Will Be Used or Disclosed?

Your child's health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, perinatal and birth records, physical examinations, laboratory records, respiratory records, nursing records, vital signs, x-rays, ultrasounds, MRIs, medication records, psychometric parameters, visual function and acuity, and auditory function may be used or disclosed in connection with this research study.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your child's health information in connection with this research study:

- The Protocol Director, David Stevenson, MD
- The Assistant Protocol Directors, Susan Hintz, MD and Krisa Van Meurs, MD
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- The research coordinator, nurses, research assistants and data clerk

Who May Receive / Use the Information?

The parties listed in the preceding paragraph may disclose your child's health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- The National Institutes of Health
- Research Triangle Institute (data management center)

Your child's information may be redisclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your child's health information will continue until December 31, 2100.

Will access to my child's medical record be limited during the study?

To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you

would have access to such health information if it was used to make medical or billing decision about your child (e.g., if included in your official medical record).

_____ _____

Signature of Legally Authorized Representative Date

_____

Description of Representative's Authority to Act for Subject

From: Neil Finer
To: "Susan Hintz"
Cc: "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"
Subject: RE: SUPPORT and secondary
Date: Friday, April 29, 2005 2:35:22 PM

Thanks Susan
Let's get your manual developed and start enrolling in your secondary. I would also suggest re-surveying the units to see who can participate.
Regards
Neil

-----Original Message-----
From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Friday, April 29, 2005 10:20 AM
To: Higgins, Rosemary (NIH/NICHD)
Cc: nfiner@ucsd.edu; aaf2@po.cwru.edu; bkh@rti.org; edward.donovan@cchmc.org; poo@rti.org; mcw3@po.cwru.edu; sduara@miami.edu; wrich@ucsd.edu; William_Oh@brown.edu
Subject: RE: SUPPORT and secondary

Hi Rose,

In the SUPPORT Neuroimaging secondary protocol, I included a statement of the need to collect these data to attempt to delineate the potential independent contribution of early hypotension (purported to be a cause of cerebral hypoperfusion leading to focal or diffuse brain injury) to abnormalities on brain MRI. I believe the best place to add those questions would be on the SUPPORT data forms - since some centers will not be enrolling in the Neuroimaging secondary until much later in the patient's hospitalization, it may be very difficult for the research nurses/coordinators to sift back through the early chart.

Also, Dr. Oh had made the point in the GDB retreat that this could be important information for the GDB overall, although the GDB subcommittee eventually had to decline adding the questions to keep the GDB a reasonable size. Dr. Finer also seemed very interested in including these kinds of questions -

Susan

>Hi all, If there is a strong desire on the part of folks to include a
>collection of BP support/volume support/hydrocortisone use, we would like a
>short hypothesis drive protocol.
>Thanks
>Rose
>
>-----Original Message-----
>From: Neil Finer [mailto:nfiner@ucsd.edu]
>Sent: Thursday, April 28, 2005 5:01 PM
>To: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; Higgins,
>Rosemary (NIH/NICHD); 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz
Duara';
>'Wade Rich'

>Subject: FW: SUPPORT and secondary
>
>Hi
>If you have time can you glance at this? We have a request to add to our
>data forms.
>I actually also would like this data for other reasons.
>Talk to you in the AM.
>Neil
>
>-----Original Message-----
>From: Susan Hintz [mailto:srhintz@stanford.edu]
>Sent: Thursday, April 28, 2005 10:21 AM
>To: nfiner@ucsd.edu
>Subject: RE: SUPPORT and secondary
>
>Sorry Neil - thought I had attached it. Here it is -
>
>Susan
>>Hi Susan
>>I would also be very interested in having this information. There was no
>>info in your email regarding Bill Oh's suggestion from the GDB retreat.
Can
>>you send that? I am very interested in the hydrocortisone issue.
>>Thanks
>>Neil
>>
>>-----Original Message-----
>>From: Susan Hintz [mailto:srhintz@stanford.edu]
>>Sent: Thursday, April 28, 2005 8:45 AM
>>To: neil finer
>>Subject: SUPPORT and secondary
>>
>>Hi Neil,
>>
>>I understand you are revising the SUPPORT data forms. As you know, I
>>had hoped to have some question on the secondary data collection
>>instrument about need for intervention for hypotension in the first
>>24 hours after delivery, but given that some sites will not be
>>enrolling in the secondary until near term (for the late US and MRI),
>>it would be difficult for research nurses/coordinators to sift back
>>through all the notes. So, could you consider adding something to
>>your forms? At the GDB retreat, Bill Oh had proposed a series of
>>questions for hypotension within 12 hours, but I thought something
>>very simple would suffice, for example:
>>
>>At any time during the first 24 hours after delivery, were any of the
>>following administered for treatment of hypotension (mark all that
>>apply)?
>>
>>____Crystalloid or colloid bolus infusion greater than 30 ml/kg
>>____Dopamine infusion at >= 10 mcg.kg/min
>>____Dobutamine infusioon at >= 10 mcg/kg/min
>>____Epinephrine continuous infusion at >=25 ng/kg/min
>>____Hydrocortisone
>>____NONE
>>
>>Let me know what you think. I have attached Bill Oh's suggestions

>>from the GDB retreat as well.
>>
>>Thanks
>>
>>Susan
>>--
>>Susan R. Hintz, M.D.
>>Assistant Professor of Pediatrics
>>Division of Neonatal and Developmental Medicine
>>Stanford University School of Medicine
>>750 Welch Road, Suite 315
>>Palo Alto, CA 94304
>>ph: 650-723-5711
>>fax: 650-725-8351
>
>
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>ph: 650-723-5711
>fax: 650-725-8351

From: William Oh
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; Ken Poole; Michele; Shahnaz Duara; Wade Rich; Susan Hintz
Subject: RE: SUPPORT and secondary
Date: Friday, April 29, 2005 12:59:59 PM

Hi all: Some of you on the GDB committee may recall that I proposed the blood pressure/volume infusion/hydrocotisone items to be added to the form. The GDB group felt that this is an issue that can be addressed by a separate time limited protocol. I think Support trial is an ideal setting for such a mini protocol. It will test the hypothesis that hypotension that requires support during the early hours will have an interactive effect on the incidence of BPD in this high risk population. I would suggest that Susan develops such a protocol. Alternatively, I would be more than happy to do so.

Bill

William Oh,MD
Professor of Pediatrics
Brown Medical School
Attending Neonatologist
Women and Infants' Hospital
101 Dudley St., Providence,RI, 02905
Phone (w) 401 274 1122 ext.1432
Fax 401 453 7571
cell 401 714 1199

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 29, 2005 12:50 PM
To: nfiner@ucsd.edu; 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; 'Ken Poole'; 'Michele'; 'Shahnaz Duara'; 'Wade Rich'; Susan Hintz; William Oh
Subject: RE: SUPPORT and secondary

Hi all, If there is a strong desire on the part of folks to include a collection of BP support/volume support/hydrocortisone use, we would like a short hypothesis drive protocol.
Thanks
Rose

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From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, April 28, 2005 5:01 PM
To: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; Higgins, Rosemary (NIH/NICHD); 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'
Subject: FW: SUPPORT and secondary

Hi
If you have time can you glance at this? We have a request to add to our data forms.

I actually also would like this data for other reasons.
Talk to you in the AM.
Neil

-----Original Message-----
From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Thursday, April 28, 2005 10:21 AM
To: nfiner@ucsd.edu
Subject: RE: SUPPORT and secondary

Sorry Neil - thought I had attached it. Here it is -

Susan
>Hi Susan
>I would also be very interested in having this information. There was
>no info in your email regarding Bill Oh's suggestion from the GDB
>retreat. Can you send that? I am very interested in the hydrocortisone
issue.
>Thanks
>Neil
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>From: Susan Hintz [mailto:srhintz@stanford.edu]
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>To: neil finer
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>it would be difficult for research nurses/coordinators to sift back
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>forms? At the GDB retreat, Bill Oh had proposed a series of questions
>for hypotension within 12 hours, but I thought something very simple
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>following administered for treatment of hypotension (mark all that
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>____Dopamine infusion at >= 10 mcg.kg/min ____Dobutamine infusioon at
>>= 10 mcg/kg/min ____Epinephrine continuous infusion at >=25 ng/kg/min
>____Hydrocortisone ____NONE
>
>Let me know what you think. I have attached Bill Oh's suggestions from

>the GDB retreat as well.
>
>Thanks
>
>Susan

>--
>Susan R. Hintz, M.D.
>Assistant Professor of Pediatrics
>Division of Neonatal and Developmental Medicine Stanford University
>School of Medicine 750 Welch Road, Suite 315 Palo Alto, CA 94304
>ph: 650-723-5711
>fax: 650-725-8351

--
Susan R. Hintz, M.D.
Assistant Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

From:	Wade Rich
To:	nfiner@ucsd.edu; "Michele Walsh-Sukys"; "Edward Donovan"; "Duara, Shahnaz"; Higgins, Rosemary (NIH/NICHD) [E]
Cc:	"Wally Carlo, M.D."
Subject:	RE: Support Pilot Vs. Main Trial
Date:	Friday, April 29, 2005 10:31:02 AM

Dr. Carlo et al. ,

It is important to remember that the unblinded oximeters which were sent out in August 2004 for the Pilot trial (noted as P16 and P17) have a different seperation algorithm than those which eventually went into the main trial.(widened 12/13/2004). The seperation we achieve with these units will not be equivalent to those currently being used for the main trial.

Wade

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Friday, April 29, 2005 6:59 AM
To: wrich@ucsd.edu
Subject: FW: Support Pilot Vs. Main Trial

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, April 28, 2005 11:34 AM
To: nfiner@ucsd.edu; Michele Walsh; Avroy A. Fanaroff, M.D.; Edward Donovan; Ed Donovan; Shahnaz; Higgins, Rosemary (NIH/NICHD)
Subject: FW: Support Pilot Vs. Main Trial

Dear All: Monica has put together this plan for our call to address what has to be done to continue the O2 sat pilot. Wally

---

From: Monica Collins
Sent: Thursday, April 28, 2005 11:19 AM
To: Wally Carlo, M.D.
Cc: bkh@rti.org
Subject: Support Pilot Vs. Main Trial

Wally,
I have put together the points in the similarities and differences in the two trials and suggestions to incorporate the pilot into the main trial. It would be a shame and waste of time, effort, and money if the trial were to stop. I understand that we may not be able to utilize the data that had been collected previously because of the oximeter differences, but otherwise, RTI has used a lot of manpower and expertise in designing the trial. And, if all centers do not want to participate, I don't see a real problem--it will just take longer. I would like for those centers who will not participate to say so upfront.
Monica

From:	Neil Finer
To:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"
Subject:	FW: SUPPORT and secondary
Date:	Thursday, April 28, 2005 5:01:30 PM
Attachments:	hypotension.doc

Hi
If you have time can you glance at this? We have a request to add to our data forms.
I actually also would like this data for other reasons.
Talk to you in the AM.
Neil

-----Original Message-----
From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Thursday, April 28, 2005 10:21 AM
To: nfiner@ucsd.edu
Subject: RE: SUPPORT and secondary

Sorry Neil - thought I had attached it. Here it is -

Susan
>Hi Susan
>I would also be very interested in having this information. There was no
>info in your email regarding Bill Oh's suggestion from the GDB retreat. Can
>you send that? I am very interested in the hydrocortisone issue.
>Thanks
>Neil
>
>-----Original Message-----
>From: Susan Hintz [mailto:srhintz@stanford.edu]
>Sent: Thursday, April 28, 2005 8:45 AM
>To: neil finer
>Subject: SUPPORT and secondary
>
>Hi Neil,
>
>I understand you are revising the SUPPORT data forms. As you know, I
>had hoped to have some question on the secondary data collection
>instrument about need for intervention for hypotension in the first
>24 hours after delivery, but given that some sites will not be
>enrolling in the secondary until near term (for the late US and MRI),
>it would be difficult for research nurses/coordinators to sift back
>through all the notes. So, could you consider adding something to
>your forms? At the GDB retreat, Bill Oh had proposed a series of
>questions for hypotension within 12 hours, but I thought something
>very simple would suffice, for example:
>
>At any time during the first 24 hours after delivery, were any of the
>following administered for treatment of hypotension (mark all that
>apply)?
>
>____Crystalloid or colloid bolus infusion greater than 30 ml/kg
>____Dopamine infusion at >= 10 mcg.kg/min
>____Dobutamine infusioon at >= 10 mcg/kg/min

>____Epinephrine continuous infusion at >=25 ng/kg/min
>____Hydrocortisone
>____NONE
>
>Let me know what you think. I have attached Bill Oh's suggestions
>from the GDB retreat as well.
>
>Thanks
>
>Susan
>--
>Susan R. Hintz, M.D.
>Assistant Professor of Pediatrics
>Division of Neonatal and Developmental Medicine
>Stanford University School of Medicine
>750 Welch Road, Suite 315
>Palo Alto, CA 94304
>ph: 650-723-5711
>fax: 650-725-8351

--
Susan R. Hintz, M.D.
Assistant Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
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Palo Alto, CA 94304
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fax: 650-725-8351

Questions regarding hypotension – BILL OH proposed at GDB Retreat 2005:

****

During the first 12 hours,

1. Was blood pressure taken? Yes___ No___

If yes,

How was it done? a. arterial catheter b. dynamap c. unknown
What was the lowest value ? ____ mm Hg Age (hr) of this value ____

2. Was bolus infusion given at anytime ? Yes___ No___

If yes,

What solution was used? a Saline b. colloid c. other specify _____

3. Was pressor used? Yes___ No___

If yes,

What pressor was used? a Dopamine__ b Dobutamine__ c. Epinephrine__ d. steroid__ e. other__ specify___

From: Petrie, Carolyn
To: Petrie, Carolyn; nfiner@ucsd.edu; Duara, Shahnaz; Edward Donovan; wcarlo@peds.uab.edu; mcw3@po.cwru.edu; Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth; Das, Abhik; wrich@ucsd.edu; reverett@med.miami.edu
Cc: hsquibb@ucsd.edu; aellison@med.miami.edu; diane.timmer@cchmc.org; msumner@peds.uab.edu; axt25@po.cwru.edu; Hastings, Betty J.
Subject: RE: SUPPORT conf call Fri,
Date: Thursday, April 28, 2005 11:17:26 AM

Reminder for tomorrow's conference call:

The SUPPORT conference call is scheduled for

Friday April 29th
11:00-12:00pm ET (8:00-9:00am PT)

To join the call:
Dial Tollfree: **866-675**(b) (6)
Passcode: (b) (6) (# when prompted)

Leader: Rose Higgins

Thank you

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 902
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Trial Concurrent Enrollment with Cycled Light
Date: Wednesday, April 27, 2005 10:24:24 AM

Good idea.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, April 27, 2005 4:12 AM
To: 'Jon.E.Tyson@uth.tmc.edu'; 'nfiner@ucsd.edu'
Cc: 'goldb008@mc.duke.edu'
Subject: Re: SUPPORT Trial Concurrent Enrollment with Cycled Light

Neil,
We can discuss this on the SUPPORT call that Carolyn is in the process of scheduling.
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Tyson, Jon E <Jon.E.Tyson@uth.tmc.edu>
To: nfiner@ucsd.edu <nfiner@ucsd.edu>
CC: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; Ronald N Goldberg <goldb008@mc.duke.edu>
Sent: Tue Apr 26 19:02:59 2005
Subject: RE: SUPPORT Trial Concurrent Enrollment with Cycled Light

Neil, I am trying to think this through from both her perspective and yours. What if Dr. Brandon were willing to stratify by gestational age, rather than birth weight (a minor change that she might be willing to make), and she were willing to be sure that all her infants were randomized into SUPPORT before being randomized into her study (presumably not a problem given that randomization into SUPPORT occurs before birth)? I would think she would want--or at least be willing--to stratify by SUPPORT treatment group using the color of the oximeter (though she wouldn't know which saturation group) and the unblended respiratory treatment group.

The design of her study would be more complex and require more work on her part but it would assure her that there was no imbalance in the SUPPORT interventions that could reduce the validity of her results and assure you that there was no imbalance in light regimen that would reduce the validity of your results. To use the rationale you've heard before: to the extent that infants were in both studies, her study would tend to reduce background noise and help to increase the signal to noise ratio.

Beside the issue of validity, there is also the issue of generalizability. Because of the variation in light regimens within and between NICUs, her

study wouldn't introduce variation in exposure to light that wasn't already present (as would occur if say she was going to test a drug that had never been used in NICUs before and that might never be used again). Thus, I don't think generalizability is an issue. And to use another rationale you've heard before: though she wouldn't have many babies in the SUPPORT trial, the data from both trials might be helpful if clinical practice changed because she or other investigators showed a strong benefit of one light regimen over another. In that case, it might be nice to have even a modicum of data regarding whether the values for RR for the therapies tested in SUPPORT varied by treatment group. (By this line of thinking, it would be good if she actually had more babies in the trial.)

Does this make sense? Have I missed something important? If both she and you would like, I can advise her on any design features that you think would make the trials fully compatible or even complementary.

Jon E. Tyson, MD, MPH

Center for Clinical Research & Evidence-Based Medicine

UT Medical School at Houston

6431 Fannin St., MSB 2.106

Houston, TX 77030

voice 713-500-5651

fax 713-500-0519

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, April 26, 2005 3:09 PM
To: Tyson, Jon E
Cc: 'Higgins, Rosemary (NIH/NICHD)'; brand005@mc.duke.edu; 'Ronald N Goldberg'
Subject: RE: SUPPORT Trial Concurrent Enrollment with Cycled Light

Hi Jon

I did look at this protocol in the past and felt that because the end-points include ROP and neurodevelopment, and the fact that randomization would not balance out the SUPPORT randomization and the cycled light study, that these studies would conflict. Thus, at this site infants will be unequally allocated to cycled light and SUPPORT. In addition this study stratifies by birth weight whereas SUPPORT does so by gestational age and this would also

be a problem if one were trying to balance the allocations.

We already know that SUPPORT is complicated. Adding cycled light to the other interventions, oximeters etc may be overwhelming to the caretakers.

I am unsure of how one would analyze the data at this site with some but not all of the infants being in the SUPPORT trial, and judging the effects of the interventions on the occurrence of ROP and neurodevelopmental outcomes.

I am open to other opinions on this issue, especially yours.

Neil

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]
Sent: Tuesday, April 26, 2005 6:38 AM
To: Neil Finer
Cc: Higgins, Rosemary (NIH/NICHD); brand005@mc.duke.edu; Ronald N Goldberg
Subject: FW: SUPPORT Trial Concurrent Enrollment with Cycled Light

Neil, would you look at this in terms of whether infants could be enrolled in SUPPORT as well as this trial at Duke? On a quick read, I didn't see a problem, given all the variability within and between centers in light exposure and the stratification by center in SUPPORT.

Jon E. Tyson, MD, MPH

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Houston, TX 77030

voice 713-500-5651

fax 713-500-0519

From: Debra Brandon [mailto:brand005@mc.duke.edu]
Sent: Thursday, April 21, 2005 6:36 PM
To: Tyson, Jon E
Subject: Fw: SUPPORT Trial Concurrent Enrollment with Cycled Light

Jon, I have attached again. Let me know if you cannot open it. It is a word file. I will have it faxed tomorrow if you cannot open.

Debbie Brandon PhD, RN, CCNS
Assistant Professor and Neonatal Specialty Director
Duke University School of Nursing
Neonatal Clinical Nurse Specialist
Duke University Hospital
Box 3322 DUMC
Durham, NC 27710
919-681-3813 voicemail
919-970-(b) (6) pager
919-668-6120 fax

----- Forwarded by Debra Brandon/NurseSch/mc/Duke on 04/21/2005 07:32 PM -----

Ronald N Goldberg/Pediatrics/mc/Duke

04/21/2005 07:27 PM

To

Debra Brandon/NurseSch/mc/Duke@mc

cc

Subject

RE: SUPPORT Trial Concurrent Enrollment with Cycled Light

Deb, can you send it to Jon,please.
Ron
----- Forwarded by Ronald N Goldberg/Pediatrics/mc/Duke on 04/21/2005 06:26 PM -----

"Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu>

04/21/2005 05:49 PM

To: "Ronald N Goldberg" <goldb008@mc.duke.edu>
cc:
Subject: RE: SUPPORT Trial Concurrent Enrollment with Cycled Light

Ron, I started to read this tonight but couldn't open the file in either of the e mails that you sent. I'm not sure whether it is a problem at your end or mine (Is it a Word document? If you send it to someone in your institution, can they open it?) Could you e mail another version or if that isn't feasible or doesn't work just fax it to me (713 500 0519). Thanks.

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

From: Ronald N Goldberg [mailto:goldb008@mc.duke.edu]
Sent: Monday, April 18, 2005 8:46 AM
To: Tyson, Jon E
Subject: Fw: SUPPORT Trial Concurrent Enrollment with Cycled Light

Jon, did you get this? Can you please look at it for me as SUPPORT is upon us.
Ron
----- Forwarded by Ronald N Goldberg/Pediatrics/mc/Duke on 04/18/2005 09:25 AM -----

Ronald N Goldberg

04/05/2005 11:48 AM

To: jon.etyson@uth.tmc.edu
cc:
Subject: Fw: SUPPORT Trial Concurrent Enrollment with Cycled Light

Jon, could you please see if there is anyway we can enroll in both concurrently. Debbie is supported by an RO1. I would appreciate your sage advice.
Ron
----- Forwarded by Ronald N Goldberg/Pediatrics/mc/Duke on 04/05/2005 11:36 AM -----

Debra Brandon

03/31/2005 11:06 AM

To: Ronald N Goldberg/Pediatrics/mc/Duke@mc
cc: Michael Cotten/Pediatrics/mc/Duke@mc, Donna Ryan/NurseSch/mc/Duke@mc, Kathy J Auten/Pediatrics/mc/Duke@mc
Subject: SUPPORT Trial Concurrent Enrollment with Cycled Light

Dear Ron,

Please forward this email request for the NICHD concurrent studies committee's review.

The NICHD SUPPORT trial and my cycled light RO1 will both be enrolling preterm infants between 23 and 28 weeks gestation. In addition, both studies have ROP and long term developmental as primary outcomes. ROP is included as a outcome in my study as a safety variable, but the cycled light intervention is not expected to have any effect on development of ROP. Of more importance, the SUPPORT trial's oxygen intervention potential to affect developmental outcome overlaps with the developmental outcome of the cycled light study.

Given the number of 23-28 week infants available I have discussed the possibility of dual enrollment with Mike Cotten (chair of my DSMB) and my grant statistician. Dual enrollment appears feasible with the utilization of a randomization schema that permits equal assignment of early and late cycled light subjects in each of the 4 arms of the SUPPORT study. Duke is willing to take responsibility for developing the randomization schema. We are asking for the NICHD concurrent studies committee's support.

I have attached a copy of the cycled light protocol. Please advise and feel free to call me as needed for questions.

Thanks,

Debbie Brandon PhD, RN, CCNS
Assistant Professor and Neonatal Specialty Director
Duke University School of Nursing
Neonatal Clinical Nurse Specialist
Duke University Hospital
Box 3322 DUMC

Durham, NC 27710
919-681-3813 voicemail
919-970-(b) (6)pager
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From: Tyson, Jon E
To: nfiner@ucsd.edu
Cc: Ronald GOldberg ; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Trial Concurrent Enrollment with Cycled Light
Date: Wednesday, April 27, 2005 8:47:06 AM

I would think Dr. Brandon could be responsible for stratifying by GA for enrollment in her study.

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

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, April 26, 2005 6:31 PM
To: Tyson, Jon E
Cc: 'Ronald GOldberg '; 'Higgins, Rosemary (NIH/NICHD)'
Subject: RE: SUPPORT Trial Concurrent Enrollment with Cycled Light

Hi Jon
I am actually OK with your suggestions. If the randomization was along SUPPORT gestational strata, and was balanced at the site – I'm not sure who (RTI?) would do this, then the study would be informative to the degree that they have power. The infants of 23 and 28 weeks are not an issue. Thus there would ideally be a method of randomizing the remaining infants equally to the 4 quadrants of SUPPORT – about 25 to each quadrant if there were 40 infants of 23 and 28 weeks.
I would like to be supportive of this project as I believe it may be relevant. I agree with the issues of generalizability and know that current practice will probably create many mushrooms raised in the dark.
Thanks for your thoughts.
Please talk to Ron and the PI.
Neil

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]
Sent: Tuesday, April 26, 2005 4:03 PM
To: nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD); Ronald N Goldberg
Subject: RE: SUPPORT Trial Concurrent Enrollment with Cycled Light

Neil, I am trying to think this through from both her perspective and yours. What if Dr. Brandon were willing to stratify by gestational age, rather than birth weight (a minor change that she might be willing to make), and she were willing to be sure that all her infants were randomized into SUPPORT before being randomized into her study (presumably not a problem given that randomization into SUPPORT occurs before birth)? I would think she would want--or at least be willing--to stratify by SUPPORT treatment group using the color of the oximeter (though she wouldn't know which saturation group) and the unblended respiratory treatment group.

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From:	Michele Walsh
To:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Shahnaz Duara"; "Wade Rich"
Cc:	"Petrie, Carolyn"
Subject:	Re: Growth secondary - SUPPORT
Date:	Tuesday, April 26, 2005 12:32:51 PM

Neil:
I gave my comments to Shanaz. Briefly:
1. As Wally indicated at the SUPPORT meeting, the primary hypothesis was a bit confusing in the wording. Does higher saturation make growth better or worst? The protocol had arguments for both.
2. How does this protocol differ from the BOOST trial which had growth as a primary outcome?
3. Growth measurements would have to be specified and performed by Research RNs. I don't think clinically obtained measurements of length and HC are accurate enough for a trial.
Otherwise, I would agree that this should go forward as a seocondary. Michele
----- Original Message -----
From: "Neil Finer" <nfiner@ucsd.edu>
To: "'Avroy A. Fanaroff, M.D.'" <aaf2@po.cwru.edu>; "'Betty Hastings'" <bkh@rti.org>; "'Ed Donovan'" <Edward.Donovan@chmcc.org>; <higginsr@mail.nih.gov>; "'Ken Poole'" <poo@rti.org>; "'Michele'" <mcw3@po.cwru.edu>; "'Neil Finer'" <nfiner@ucsd.edu>; "'Shahnaz Duara'" <sduara@miami.edu>; "'Wade Rich'" <wrich@ucsd.edu>
Cc: "'Petrie, Carolyn'" <petrie@rti.org>
Sent: Saturday, April 23, 2005 4:51 PM
Subject: FW: Growth secondary - SUPPORT

> Hello Everyone
>
> I had previously sent out this response from Brenda with a request that you
> review the Growth Secondary. Please let me know your thoughts for the Growth
> Secondary. I am concerned that the email may not have gone out. We have had
> some trouble with our University server etc.
> In addition
> We are still getting replies from the sites regarding the use of hi flow NC
> on room air. At present there appears to be significant use.
> My suggestions are as follows.
> 1. We keep the study oximeter on for any respiratory support, - oxygen CPAP,
> ventilation and hi flow NC in room air as defined by a flow of => 500
> ml/min.
> 2. We record once a day for any infant on any form of support, the infants
> FiO2 and the level of any support after 14 days.
> 3. We indicate the highest FiO2 for the 24 hours and the mode or the FiO2
> that was used the most frequently for that 24 hour period. I know that we
> could collect more, but I am not sure how we would use the information.
> Your thoughts?
> I will ask Carolyn to arrange a conference call if we can for next week

> Be well
> Neil
>
> -----Original Message-----
> From: Brenda Poindexter [mailto:bpoindex@iupui.edu]
> Sent: Thursday, April 14, 2005 11:50 AM
> To: nfiner@ucsd.edu
> Subject: Growth secondary - SUPPORT
>
> Hi Neil. I looked the proposal for the growth secondary for SUPPORT over.
> Here are some brief comments:
> 1) Hypotheses/Specific Aims - I am surprised that there is no mention of
> looking at growth related to presence/absence of BPD - this will be a huge
> confounder.
> 2) Growth measurements - unless specifically stated in an interventional
> trial, the growth measurements that the Network has historically used are
> those recorded by the bedside nurse (as opposed to a more standardized
> approach using research personnel). In the glutamine trial, the 36 week
> anthropomorphic data was obtained by the research nurses. In general, I
> think the consensus is that routine bedside measurements are highly
variable
> and probably should not be used for research where growth is the outcome
of
> interest - this will change the nursing time and budget required (I don't
> think this would be prohibitive, but if this is going to done, we should
do
> it right).
> 3) Nutritional intake - the proposal to only collect nutritional intake
for
> a 24 hour period of time is, in my opinion, insufficient. I would propose
a
> similar intake collection form as what we did for glutamine. Also, we
have
> agreed to define full enteral feeds as >= to 120 /kg/d (as opposed to
> parenteral < 20/kg/d)
> 4) Post-discharge oxygen use - would incorporate a plan to collect this
data
> 5) Additional analyses - although the impact of oxygen saturation on
growth
> is certainly of interest, you will also have neurodevelopmental outcome at
> 18 months. It really is a no-brainer to also look at the correlation
> between growth and neurodevelopment.
> Hope these comments are helpful - this is an area that I am obviously
> interested in, so please don't hesitate to ask if I can be of help with
> this.
> Brenda
>
>

Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

From:	Roy Heyne
To:	drficmd@aol.com; steichji@email.uc.edu; adusick@iupui.edu; Higgins, Rosemary (NIH/NICHD) [E]; golds005@mc.duke.edu; vjohnson@med.wayne.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; MPeralta@PEDS.UAB.EDU; petrie@rti.org; mbball@stanford.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; gary_myers@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; rdillard@wfubmc.edu; bvohr@wihri.org; richard.ehrenkranz@yale.edu
Cc:	adas@rti.org; bkh@rti.org; joa@rti.org; mcclure@rti.org; poo@rti.org; schaefer@rti.org; BRUNNEMJ@UCMAIL.UC.EDU; Alice.J.Reardon@uth.tmc.edu; jrose@wihri.org
Subject:	Additional Modifications for NF03-5
Date:	Tuesday, April 26, 2005 10:13:11 AM

Here is a brief recap of the changes for NF03-04, most of which I brought up during our conference call yesterday.

NF03: C.1. "Apart from the primary caretaker....."
E.e.a.i. "If YES, in which type of Follow-up....." (did not mention this one on phone)
F.1. "Is your child taken care of by someone other than the primary caretaker?"
Note: this question presumes that the person being interviewed is a parent (natural or foster), which would be the expected scenario. However, the form does not explicitly document who is providing the
information for the form anywhere that I can see. Do we need to document this?
F.1.c.ii. Omit "full or part time" and add reference code for specification of "where"

NF04: A.2.f Regarding Betty's e-mail comment, I think fundoplication is an acceptable spelling in the literature.
A.5 Since A.2 already indicates whether the child has had a gastrostomy or tracheostomy procedure (prior to or
since discharge), it is redundant to ask here if such has been "prescribed". If we want to know if the child
still has either device, or if it has been removed, then it might be better to ask that as a part 3 column under
question 2. That would leave question 5 to deal with non-surgical treatments which are not covered under 2.
A.7 Need to have Y N responses for each of the diet items 1-3.

NF05 (didn't cover during the call)
B.4.2 Think we need to carve out the item covered in 3: "Lower extremity muscle tone excluding ankles"
B.4.3 Thought we had agreed that the joint we wanted to carve out was "Ankles" not "Knees"
B.7 The manual describes 3 reflexes one needs to check for: ATNR, positive support, and tonic labyrinthine.
However, the form only shows "ATN or TNR" I'm not sure what a TNR is supposed to be, since there are both STNR and ATNR, the former of which is considered unreliable. I would suggest the following
wording: "ATNR, TLR, or PS" to match the narrative description in the manual. (These are also the reflexes
used in the BEAM exam). Though the TLR comes in several different forms (prone/supine, extension/flexion)
I don't think we need to get that specific here.
B.16 If we are going to have RTI calculate the Motor Quotient, then the form needs to include some explicit way of
specifying the highest milestone accomplished, or, better yet, of checking all the milestones the child can do. In
the case of the dual 4 month and 5 month milestones, it needs to be clear that the child must be able to do both
of the milestones for each of these ages in order to get credit for that motor age.

Finally, just a clarification regarding how B.1 and B.2 are used by RTI: Are B.1.d. and 2.c the basis for determing
whether the child has blindness or hearing requiring aids as elements of the overall category of "NDI"? If so,

are
we presuming the child has had some formal ophthalmological and/or audiological evaluation to confirm the examiner's
"clinical" assessment?

>>> "Petrie, Carolyn" <petrie@rti.org> 04/25/05 2:03 PM >>>
Reminder:

The next Follow Up form review call to discuss the NF09, NF10 and NF10A:

Monday, April 25th

3:00-4:00pm ET (12:00-1:00pm PT)

To join the call:

Dial Tollfree: 866-675(b) (6)

Passcode: (b) (6) (# when prompted)

Leader: Rose Higgins

Thank you,

Carolyn Petrie

Neonatal Research Network Coordinator

RTI International

6110 Executive Blvd

Suite 902

Rockville, MD 20852

ph. (301) 230-4648

fx. (301) 230-4646

From: Tyson, Jon E
To: Neil Finer
Cc: Higgins, Rosemary (NIH/NICHD) [E]; brand005@mc.duke.edu; Ronald N Goldberg
Subject: FW: SUPPORT Trial Concurrent Enrollment with Cycled Light
Date: Tuesday, April 26, 2005 9:38:02 AM
Attachments: CL vs. ND RO1 feb 2002 Final.doc

Neil, would you look at this in terms of whether infants could be enrolled in SUPPORT as well as this trial at Duke? On a quick read, I didn't see a problem, given all the variability within and between centers in light exposure and the stratification by center in SUPPORT.

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

From: Debra Brandon [mailto:brand005@mc.duke.edu]
Sent: Thursday, April 21, 2005 6:36 PM
To: Tyson, Jon E
Subject: Fw: SUPPORT Trial Concurrent Enrollment with Cycled Light

Jon, I have attached again. Let me know if you cannot open it. It is a word file. I will have it faxed tomorrow if you cannot open.

Debbie Brandon PhD, RN, CCNS
Assistant Professor and Neonatal Specialty Director
Duke University School of Nursing
Neonatal Clinical Nurse Specialist
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Box 3322 DUMC
Durham, NC 27710
919-681-3813 voicemail
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919-668-6120 fax

----- Forwarded by Debra Brandon/NurseSch/mc/Duke on 04/21/2005 07:32 PM -----

Ronald N Goldberg/Pediatrics/mc/Duke

04/21/2005 07:27 PM

To Debra Brandon/NurseSch/mc/Duke@mc

cc

Subject RE: SUPPORT Trial Concurrent Enrollment with Cycled Light

Deb, can you send it to Jon,please.

Ron
----- Forwarded by Ronald N Goldberg/Pediatrics/mc/Duke on 04/21/2005 06:26 PM -----
"Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu>

04/21/2005 05:49 PM

To: "Ronald N Goldberg" <goldb008@mc.duke.edu>
cc:
Subject: RE: SUPPORT Trial Concurrent Enrollment with Cycled Light

Ron, I started to read this tonight but couldn't open the file in either of the e mails that you sent. I'm not sure whether it is a problem at your end or mine (Is it a Word document? If you send it to someone in your institution, can they open it?) Could you e mail another version or if that isn't feasible or doesn't work just fax it to me (713 500 0519). Thanks.

Jon E. Tyson, MD, MPH
Center for Clinical Research & Evidence-Based Medicine
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From: Ronald N Goldberg [mailto:goldb008@mc.duke.edu]
Sent: Monday, April 18, 2005 8:46 AM
To: Tyson, Jon E
Subject: Fw: SUPPORT Trial Concurrent Enrollment with Cycled Light

Jon, did you get this? Can you please look at it for me as SUPPORT is upon us.
Ron
----- Forwarded by Ronald N Goldberg/Pediatrics/mc/Duke on 04/18/2005 09:25 AM -----
Ronald N Goldberg

04/05/2005 11:48 AM

To: jon.etyson@uth.tmc.edu
cc:
Subject: Fw: SUPPORT Trial Concurrent Enrollment with Cycled Light

Jon, could you please see if there is anyway we can enroll in both concurrently. Debbie is supported by an RO1. I would appreciate your sage advice.
Ron
----- Forwarded by Ronald N Goldberg/Pediatrics/mc/Duke on 04/05/2005 11:36 AM -----

Debra Brandon

03/31/2005 11:06 AM

To: Ronald N Goldberg/Pediatrics/mc/Duke@mc
cc: Michael Cotten/Pediatrics/mc/Duke@mc, Donna Ryan/NurseSch/mc/Duke@mc, Kathy J Auten/Pediatrics/mc/Duke@mc
Subject: SUPPORT Trial Concurrent Enrollment with Cycled Light

Dear Ron,

Please forward this email request for the NICHD concurrent studies committee's review.

The NICHD SUPPORT trial and my cycled light RO1 will both be enrolling preterm infants between 23 and 28 weeks gestation. In addition, both studies have ROP and long term developmental as primary outcomes. ROP is included as a outcome in my study as a safety variable, but the cycled light intervention is not expected to have any effect on development of ROP. Of more importance, the SUPPORT trial's oxygen intervention potential to affect developmental outcome overlaps with the developmental outcome of the cycled light study.

Given the number of 23-28 week infants available I have discussed the possibility of dual enrollment with Mike Cotten (chair of my DSMB) and my grant statistician. Dual enrollment appears feasible with the utilization of a randomization schema that permits equal assignment of early and late cycled light subjects in each of the 4 arms of the SUPPORT study. Duke is willing to take responsibility for developing the randomization schema. We are asking for the NICHD concurrent studies committee's support.

I have attached a copy of the cycled light protocol. Please advise and feel free to call me as needed for questions.

Thanks,

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A. SPECIFIC AIMS

Preterm infants' growth and developmental outcomes vary with illness and degree of neurological insult (Morris, 1999; Vohr et al., 2000), yet unpredictable variations in outcomes exist even among the healthiest preterm infants (Huber, Holditch-Davis, & Brandon, 1993). These variations have led to speculation that the neonatal intensive care unit (NICU) environment, and light in particular, may affect outcomes, especially for infants requiring extensive hospitalization ($\leq$ 28 weeks gestation) (Blackburn, 1998; Graven et al., 1992). The fetus develops in a rich circadian environment, including maternal hormones and rest-activity cycles while remaining in near darkness, but the NICU environment provides limited circadian cues and significant light exposure depending upon individual nursery practices.

Previous research on light exposure suggests that cycled light and continuous near darkness are both more beneficial in promoting health and development in preterm infants than continuous bright light (Blackburn & Patterson, 1991; Glotzbach et al., 1991; Mann et al., 1986; Miller et al., 1995). However, only recently has cycled light been compared to near darkness to ascertain which of these two is more beneficial for health and development (Brandon, 2000; Brandon et al., 2002; Miramin & Ariangno, 2000). The findings suggest that early cycled light is more beneficial than extended near darkness followed by cycled light, but it remains unclear at what gestational age cycled light should be initiated. Some evidence suggests that 28-weeks gestational age may be the time when the visual sensory system is capable of handling light stimulation, since at this point the brain has established a full complement of neurons, migration and differentiation of neurons are beginning, and the suprachiasmatic nuclei (SCN) are innervated by the retina and responsive to light (Hao & Rivkees, 1999; Isenberg, 1994). In addition, for infants born at an average gestational age of 28 weeks, cycled light from birth has been found to result in significantly better weight gain than cycled light beginning at 36 weeks post-conceptional age (PCA) (Brandon, 2000; Brandon et al., 2002).

The purpose of the proposed study is to determine the appropriate time for instituting cycled light for the youngest preterm infants ($\leq$ 28 weeks gestation at birth). A longitudinal randomized two-group design will be used to evaluate the effects of early (28 weeks) and late (36 weeks) cycled light on short- and long-term health and developmental outcomes including sleep-wake state development, weight gain, lung maturation, length of hospitalization (LOS), auditory and visual development, and neurodevelopmental outcomes (see Figure 1, pg.). Based on the investigator's previous work, the following hypotheses will be tested:

As compared to infants receiving late cycled light (at 36 weeks PCA), infants receiving early cycled light (at 28 weeks PCA) will:

1. have significantly more organized sleep-wake states before and after hospital discharge, after covarying the effects of medical complications **known to affect sleep wake patterns (intraventricular hemorrhage [IVH], birth weight, caffeine, and length of mechanical ventilation);**
2. gain weight significantly faster before and after hospital discharge, after covarying the **known effects of birth weight;**
3. have significantly fewer hospital days, **when the effects of severity of illness and birth weight known to influence length of mechanical ventilation and hospitalization are covaried;**
4. develop retinopathy of prematurity (ROP) significantly more slowly, **after covarying effects of medical complications known to affect ROP (IVH, length of mechanical ventilation);**
5. have significantly better visual acuity (preferential looking test) at 12 months corrected age, **after covarying the known effects of birth weight and severity of ROP;**
6. have significantly better neurological outcomes at 9 and 18 months corrected age;
7. have significantly better developmental outcomes (cognitive, motor, and language) at 9 and 18 months corrected age.

Infants in the two different light groups are not expected to differ in the incidence of abnormal audiological findings as measured by the brainstem auditory evoked potential (BAER), but they will be evaluated to ensure the safety of early cycled light. Light intervention effects are not expected to differ as a function of gender or ethnicity. The multiple outcomes examined will permit the investigator to evaluate the most appropriate time to initiate cycled light.

B. BACKGROUND AND SIGNIFICANCE

Preterm Infant Outcomes

Preterm infants are at greater risk for cognitive, attentional, language, motor, visual-spatial, and behavioral difficulties than healthy term infants (Bigsby et al., 1996; Cherkes-Julkowski, 1998; D'Agostino & Clifford, 1998; Huber et al., 1993; Roth et al., 2001; Vohr et al., 2000; Volpe, 1998; Wood et al., 2000). Severe developmental problems, including cognitive and motor abnormalities, are predictable for infants with major medical complications at birth (Vohr et al., 2000; Vohr & Ment, 1996; Volpe, 1998), such as grade III and IV intraventricular hemorrhage, and for infants with poor home environments (Bendersky & Lewis, 1994; Miceli et al., 2000). However, one-third of preterm infants with cerebral palsy have no identifiable medical cause (Veelken et al., 1993; Volpe, 1998); and numerous less severe developmental problems, such as attentional and visual processing difficulties, cannot be predicted for individual infants (Huber et al., 1993; Waber & McCormick, 1995). **A growing body of animal literature suggests that departures from normal or usual sensory experiences can alter subsequent development (Banker & Lickliter, 1993; Gottlieb, 1991; Kenny & Turkewitz, 1986; Lickliter, 1994; Lickliter & Lewkowicz, 1995; Radell & Gottlieb, 1992; Sleigh & Lickliter, 1998), but the mechanisms behind the altered developmental trajectories are not well understood; and the effects of altered environments have not been well studied in humans (Lickliter, 2000a; 2000b; Marshall-Baker et al., 1998). Since human sensory systems are not fully mature following preterm birth, the infant is exposed to an altered developmental environment. Thus, predictive models of preterm infant developmental outcomes need to include factors such as the NICU environment.**

The NICU light environment is one potential influence on developmental outcomes. Constant bright light has been related to an increase in infant respiratory instability (Shiroiwa et al., 1986) and less sleep and weight gain (Mann et al., 1986; Miller et al., 1995), consistent with findings on the negative consequences of constant light in the animal literature (e.g., Bellhorn, 1980). Light and visual stimulation are imperative for brain maturation and circadian rhythm development (Black, 1998; Rivkees, 2001; Rivkees & Hao, 2000; Torczynski, 1994), some light exposure in the NICU is inevitable, and cycled light is the typical environment after hospital discharge. However, the intensity and timing of cycled light that are best for preterm infants and the ways in which the light environment may affect later development, such as cognitive development, visual processing and attentional capabilities, are unknown.

Light Effects on Brain Maturation and Circadian Rhythm Development

Brain Maturation. Developmental outcomes vary with the nature of the organism and the environment in which it exists. Yet organisms are not equally vulnerable to an abnormal developmental path at every point in time (Kenny & Turkewitz, 1986; Lickliter, 2000b). The timing and quality of the environmental experience influence vulnerability (Black, 1998; Ford & Learner, 1992; Gottlieb, 1991). Neuronal development occurs when the fetal brain is exposed to expected experiences at just the right time. If expected experiences occur too early or too late, variations can occur in the development of neuronal patterning or nerve growth and their connections (Greenough et al., 1987). Sensory systems develop interdependently (Turkewitz & Kenny, 1985), but with an invariant sequence across all birds and mammals, such that the organism develops first tactile, then vestibular, then chemical, then auditory, and lastly the visual system (Gottlieb, 1971a; 1971b). **This sequence of sensory development typically limits stimuli early in development for immature sensory systems and then becomes more complex as sensory**

systems mature and become capable of handling stimulation (Turkewitz & Kenny, 1985). A growing body of literature suggests that a departure from normal or usual sensory experiences may hinder or facilitate development (Banker & Lickliter, 1993; Carlsen & Lickliter, 1999; Honeycutt & Lickliter, 2001; Lickliter, 1994, 2000a; Lickliter & Lewkowicz, 1995; Marshall-Baker et al., 1998; Radell & Gottlieb, 1992; Sleigh & Lickliter, 1998).

Since the visual system is the last to develop (Gottlieb, 1971a), it is the most immature and potentially vulnerable system at the time of preterm birth (Lickliter, 2000a). Development of the eye begins on the 22nd day of fetal life (Isenberg, 1994). By the end of the second month gestation, the retina, cornea, lens, iris, nerve cells, and optic nerve have begun the process of differentiation and migration (Isenberg, 1994). Rapid differentiation and migration of eye structures continue from the second month of gestation throughout the prenatal period. The layers of the retina have been formed by 22 weeks gestation, rods and cones are present by 23 weeks, and myelinization of the optic nerve begins at 24 weeks (Hack, 1983). The neurons forming the visual cortex are in place by 26 weeks gestation, and visual evoked potentials have been recorded as early as 24 weeks gestation (Hack, 1983; Tsuneishi & Casaer, 2000); however significant numbers of rods and cones are not functioning until 28 weeks gestation (Cepko, 1996).

Development of the visual system after birth occurs partially in response to light stimuli (Torczynski, 1994), but it is unclear how eye development is altered by earlier than normal light stimulation (Fielder & Moseley, 2000; Tsuneishi & Casaer, 2000). One study of preterm infants suggests that the preterm experience has little effect on myelination of the visual pathways, but it alters how visual evoked potential waveforms look over the course of development (Tsuneishi & Casaer, 2000). It is unknown whether these changes in the evoked potential waveforms represent normal preterm visual development, or how the changes may relate to visual outcomes. However, it is clear that the light experience of the fetus in utero is minimal compared to that of a preterm infant in the NICU (Fielder & Moseley, 2000; Weaver & Reppert, 1989).

The absence of eye opening in utero before 28 weeks may reflect the visual structures' lack of readiness for stimulation (Isenberg, 1994; Kozuma, 1998). The absence of a blink reflex before 30 weeks means that preterm infants are unable to regulate light exposure by closing their eyes (Isenberg, 1994). Robinson and colleagues (1989) found that in constant light environments, very immature (24-25 weeks gestation) preterm infants had their eyes open approximately 45% of the time, 28 to 31 week preterm infants had their eyes open only 20% of the time, and the most mature preterm infants (31 to 35 weeks) had their eyes open 40% of the time. This suggests that preterm infants have difficulty shutting out light before 28 weeks, but their visual system may be capable at that point of handling low intensity cycled light.

<u>Circadian Rhythms.</u> **Although the extent to which the fetal circadian system is mature is unknown, the fetus clearly develops in a circadian environment with day-night differentiation. While the intrauterine environment is mostly dark, it is rich with circadian rhythm cues provided by the mother, such as sleep-activity, meal, and hormonal patterns; and the human fetus exhibits circadian rhythms in heart rate, respiratory rate, and adrenal steroidogenesis (Rivkees & Reppert, 1992; Seron-Ferre et al., 1993). Following preterm delivery, it is not possible to provide intrauterine circadian cues, but promotion of circadian rhythms is thought to be important to the health and development of preterm infants (Rivkees, 2001; Rivkees & Hao, 2000). Indeed, in older children circadian rhythms have a recognized role in the efficacy of medical therapies, including response to asthma drugs and accurate determination of laboratory values (Moore-Ede et al., 1983).** Several studies have described the development of rhythmicities in hospitalized preterm infants (Glotzbach et al., 1991; Holditch-Davis & Edwards, 1998b; McMillen et al., 1991; Mirmiran & Kok, 1991; Tenreiro et al., 1991; Thomas, 1991). Prior to discharge, preterm infants have demonstrated ultradian rhythms (short rhythms a few hours long) in heart rate, respiratory rate, blood pressure, and sleep-wake state, and circadian rhythms in temperature (Glotzbach, et al., 1995; Holditch-Davis & Edwards, 1998b; Thomas, 1991). One study showed few circadian rhythms in extreme preterm infants who were fed continuously and had constant ambient lighting (Tenreiro et al., 1991).

However, these infants demonstrated an increased circadian rhythmicity in heart rate after they were placed in a nursery that dimmed the lights at night. Another study identified temperature cycles of 2, 3, and 6 hours in preterm infants that did not appear to be related to incubator air temperature (Thomas, 1991). Several studies have demonstrated that these rhythmicities in preterm infants were related to environmental events, such as feeding and nurse caregiving (Glotzbach et al., 1995; McMillen et al., 1991; Rivkees et al., 1997), but since the infants were cared for in constant light environments, either continuous near darkness or continuous light, the effects of cycled light were not addressed.

Day and night cycling of light is one of the few day-night differentiations that can be easily experienced by preterm infants, and it will be the typical environment for the preterm infant following hospital discharge. The effect of light on the development of biological rhythms has been studied extensively (e.g., Edgar & Fuller, 1993; Hofman & Swaab, 1992; Rivkees, 1997; Sadun et al., 1984; Schwartz et al., 1986), but less is known about the effect of light on prenatal or preterm infant development (Hao & Rivkees, 1999; Rivkees & Hao, 2000). The biological clock, the suprachiasmatic nuclei (SCN), has been identified as early as 18 weeks gestation in humans (Reppert et al., 1988), and the retinohypothalamic tract (light input pathway) to the SCN has been identified in one human at 36 weeks gestation (Glotzbach et al., 1992). Preterm baboons have SCN innervated by the retina and responsive to light at an age thought to be comparable to 25 weeks human gestation (Hao & Rivkees, 1999; Rivkees et al., 1997). Thus, the preterm infant may be able to receive light stimuli to the SCN by 25 weeks gestation, and light in the NICU environment may affect sleep-wake state development, growth, visual outcomes, auditory outcomes, and neurodevelopmental outcomes.

Effects of Light on Preterm Outcomes

Sleep. The developmental sleep patterns of term infants are quite different from preterm infants (Ardura, et al., 1995; Davis & Thoman, 1987). Sleeping and waking states change over the preterm period as the brain matures (Holditch-Davis, 1990a; Holditch-Davis & Edwards, 1998a; Ingersoll & Thoman, 1999); the major developmental changes include a decrease in the amount of active sleep, increases in quiet sleep and waking states, and an increase in the organization of sleep states (Holditch-Davis, 1990a; Holditch-Davis & Edwards, 1998; Vles et al., 1992). Preterm infants, at term age, spend more time in quiet sleep, exhibit more movements during sleep, and are alert more when alone than term infants (Davis & Thoman, 1987). The altered preterm sleep-wake patterns continue for several months and may impact not only infant recovery and health but also parent-infant interactions (Ardura et al., 1995; Miller & Holditch-Davis, 1992). Ardura et al. (1995) found that at 30 days after term age, preterm infants slept more than term infants but did not develop more nocturnal sleep than daytime sleep. This lack of a circadian sleep pattern in preterm infants could be related to the early, non-cycled-light environment experienced in the NICU.

However, in the extensive research on the development of sleeping and waking states in preterm infants, the influence of the light environment has not usually been examined (Curzi-Dascalova et al., 1988; Holditch-Davis, 1990a; 1990b; Holditch-Davis & Edwards, 1998; Parmelee & Stern, 1972; Parmelee et al., 1967; Prechtl et al., 1979). The majority of sleep-wake state development research has been done in constant lighting conditions (the few studies evaluating the effects of different lighting conditions are discussed below). Studies done in constant light environments have found that preterm infants' sleep-wake states are more poorly organized than those of fullterm infants and more difficult to interpret (High & Gorski, 1985; Holditch-Davis, 1990a; Holditch-Davis & Edwards, 1998; Prechtl et al., 1979). Yet organized sleep is important for the health and development of humans (Hobson, 1993).

One study examining the effect of cycled light on sleep in hospitalized preterm infants revealed both an increase in the total amount of quiet sleep and longer bouts of quiet sleep when the infants received cycled light (Blackburn & Patteson, 1991). Another study demonstrated that infants with just four scheduled "nap" times in a darkened incubator experienced significantly more sleep, less activity and longer sleep periods, and less activity during naps (Holditch-Davis et al., 1995). In a group of convalescent preterm infants (mean

gestational age > 31 weeks), Mann et al. (1986) found that infants in cycled light and with noise reduction strategies slept more than infants in constant bright light without any attempts at noise reduction.

Growth. More than anything else, weight is the factor that determines infant length of hospital stay. Two studies (Mann et al., 1986; Miller et al., 1995) have demonstrated the advantages of cycled light over constant bright light in regard to weight gain. Mann et al. (1986) found that infants in cycled light with reduced noise exposure exhibited more weight gain and spent less time feeding than infants exposed to constant bright light and noise. In Miller et al.'s study (1995), infants with a mean gestational age of 28 weeks received either continuous bright light or cycled light. Infants in the cycled-light group gained more weight, were fed orally sooner, and had fewer ventilator days. Only one study has looked at outcomes of cycled light after discharge from the hospital (Mann et al., 1986). In that study, preterms who experienced cycled light in the NICU gained weight faster, slept more after discharge, and spent less time feeding than preterms who experienced continuous light. The authors concluded that these differences could have resulted from a variety of biological factors, including hastening of circadian rhythm development by cycled light.

Visual. To date, research on the effects of light on preterm visual outcomes has primarily looked at the development of retinopathy of prematurity (ROP), a progressive disease of the retina that if untreated results in sclerosis of the vascularity, scaring, retinal detachment, and eventual blindness (O'Conner, 1999). Approximately 84% of infants born at < 28 weeks gestation will develop some degree of ROP, but fortunately most ROP (80%) resolves without visual loss from retinal detachment or scars (Cryotherapy Group, 1994). Between 2% and 4% of infants born at ≤ 26 weeks may lose all of their vision secondary to ROP (Phelps, 1995). The risk for ROP and the severity of the disease are related to the degree of prematurity and the severity of respiratory disease, but the cause of ROP has not been determined. However, ROP has been related to oxygen exposure, wide swings in oxygenation, hypoxia, free radicals and light exposure (Phelps et al., 2000).

There have been conflicting reports about the effect of light on the development of ROP (Ackerman et al., 1989; Glass et al., 1985; Seiberth et al., 1994). In an early study, Glass et al. (1985) found a higher incidence of ROP in preterm infants exposed to continuous bright light, especially infants with birth weights <1000 grams, and they hypothesized that light may cause alterations in retinal metabolism, including the introduction of free radicals, which could result in the changes in retinal vascularity and scaring seen in ROP. Three more recent studies (Ackerman et al., 1989; Reynolds et al., 1998; Seiberth et al., 1994), however, found no differences in the incidence of ROP when infants were shielded from light. In Seiberth and colleagues' study, the control group did not receive continuous bright light but cycled light. The period of near darkness provided by the cycled light may have enabled retinal photoreceptors to recover, or the light may have promoted retinal maturation. Also, in preliminary work for the proposed study (see Preliminary Studies; Brandon et al., 2002 Appendix A-1), infants exposed to cycled light from birth appeared to develop ROP slower than infants exposed to continuous near darkness until 36 weeks post-conceptional age.

Auditory. **Animal studies have revealed altered development with sensory stimulation that is atypical for the organism, but the mechanisms behind the altered developmental trajectories are not well known. Birds demonstrate limitations in the ability to recognize their maternal call following hatching when they receive early prenatal visual stimulation (Radell & Gottlieb, 1992), but it is unclear whether the mechanism of the altered auditory learning is delayed maturation of the auditory system or something else. Therefore, it is possible that sensory deprivation or enhancement of a late developing system such as vision could result in acceleration, deceleration, or no change in the development of an earlier developing system such as audition.**

Few studies have looked at the effects of altered environments on humans (Lickliter, 2000a; 2000b; Marshall-Baker et al., 1998). Early light exposure and visual stimulation have been found to facilitate visual development, promote behavioral organization, or delay maturation of auditory development depending upon when the stimulation occurred (Brandon, 2002, see Appendix A;

Gottlieb et al., 1989; Marshall-Baker et al., 1998). Brandon et al. (2002) found more auditory acuity failures when cycled light stimulation began at 32 weeks gestational age, than when cycled light began before 31 weeks or at 36 weeks PCA (see Preliminary Studies). These differences in auditory acuity, however, disappeared on repeat auditory assessments after discharge, indicating that there may have been a delay in maturation of auditory development with poorly timed (32-week) cycled light stimulation.

Neurodevelopmental Outcomes. Als et al. (1986) have proposed an environment of near darkness for preterm infants until they are discharged from the hospital, regardless of their age, along with strategies for reduction of noise and other noxious stimuli in the environment. Investigators taking this approach have found short- and long-term positive effects on behavioral organization, oxygen saturation and developmental outcomes, but because the studies examined outcomes of an entire developmental program, the effects of near darkness alone are not known (Als, 1995; Als et al., 1986; Becker et al., 1993). Like constant bright light, constant near darkness does not promote development of circadian rhythms (Rivkees, 2000; 1997).

Studies that have found positive effects of cycled light on the neonate have primarily used continuous bright light for the control group (Blackburn & Patteson, 1991; Mann et al., 1986; Miller et al., 1995). Near darkness only recently has been studied as a separate intervention (see Preliminary Studies; Brandon et al., 2002, Appendix A; Mirmiran & Ariagno, 2000). Mirmiran and Ariagno (2000) found no differences between infants receiving cycled light and near darkness in the development of circadian rhythms in body temperature at 36 weeks PCA and 1 and 3 months corrected age, but these infants were not under cycled light conditions until they were medically stable, and some infants received only 2 weeks of the cycled light prior to discharge. Previous work by the principal investigator (see Preliminary Studies; Brandon et al., 2002, Appendix A) suggests that prolonged near darkness may be less beneficial than cycled light, depending upon when the cycled light is initiated. Therefore, the proposed study will determine the appropriate time to introduce cycled light to the youngest preterm infants ($\leq$ 28 weeks gestation) to maximize their short- and long-term health and developmental outcomes.

Theoretical Framework

Developmental scientists view development as a complex, multi-causal, non-linear, always changing system (Cairns et al., 1996; Gottlieb, 1997; 1996; 1991; Sameroff, 1983; Thelen & Smith, 1994). The framework for the study (represented in Figure 1) utilizes a developmental systems approach. The outcome variables are organized from short to long-term outcomes, for sleep-wake states, which is both a short- and long-term variable. Developmental outcomes vary with the nature of the organism and the environment in which it exists. Following preterm delivery, the expected developmental experiences of the intrauterine environment are greatly altered, possibly resulting in a different developmental path (Cairns et al., 1996; Greenough et al., 1987). The NICU environment exposes the preterm infant to sensory experiences that are decreased, increased, or absent in the intra-uterine environment. Since the altered light experience may hinder or facilitate different outcomes, multiple outcomes must be considered to determine the most appropriate time to introduce cycled light.

Day and night cycling of light is clearly essential to the development of normal circadian rhythms (Rivkees, 1997) and it can be achieved with low intensity illumination (Rivkees et al., 1997) (see Figure 1, pg). While the timing of circadian system maturation is unknown (Rivkees, 1997), we know that the fetus develops in a day-night environment provided by the mother (Rivkees & Reppert, 1992; Seron-Ferre et al., 1993), and term infants in a cycled light environment demonstrate circadian rhythms in body temperature by 1 week of age (McGraw et al., 1999). Exposure to cycled light after fullterm delivery is instrumental in the development of circadian rhythms (McGraw et al., 2000; Mirmiran & Kok, 1991; Recio et al., 1997). Preterm infants appear to have delayed maturation of circadian rhythms as compared to term infants (Kennaway, 2000; Kennaway et al., 1996); and this late development of circadian rhythms may be related to lack of predictability and cycled light in the NICU environment (Mirmiran & Ariangno, 2000). Some light exposure in the NICU environment is

inevitable, cycled light following hospital discharge is typical, and by 28 weeks the preterm infant retina may be well enough developed to receive light and stimulate the SCN to promote circadian rhythms (Rivkees & Hao, 2000). Therefore, low intensity cycled light may be the best stimulus available to minimize the disruption of the maternal circadian rhythm environment. The initiation of cycled light at 28 weeks gestation is timed to reduce potential negative effects of very early light exposure on sensory development and to match when the retinohypothalamic pathway is probably functional and able to facilitate development of circadian rhythms (Rivkees & Hao, 2000).

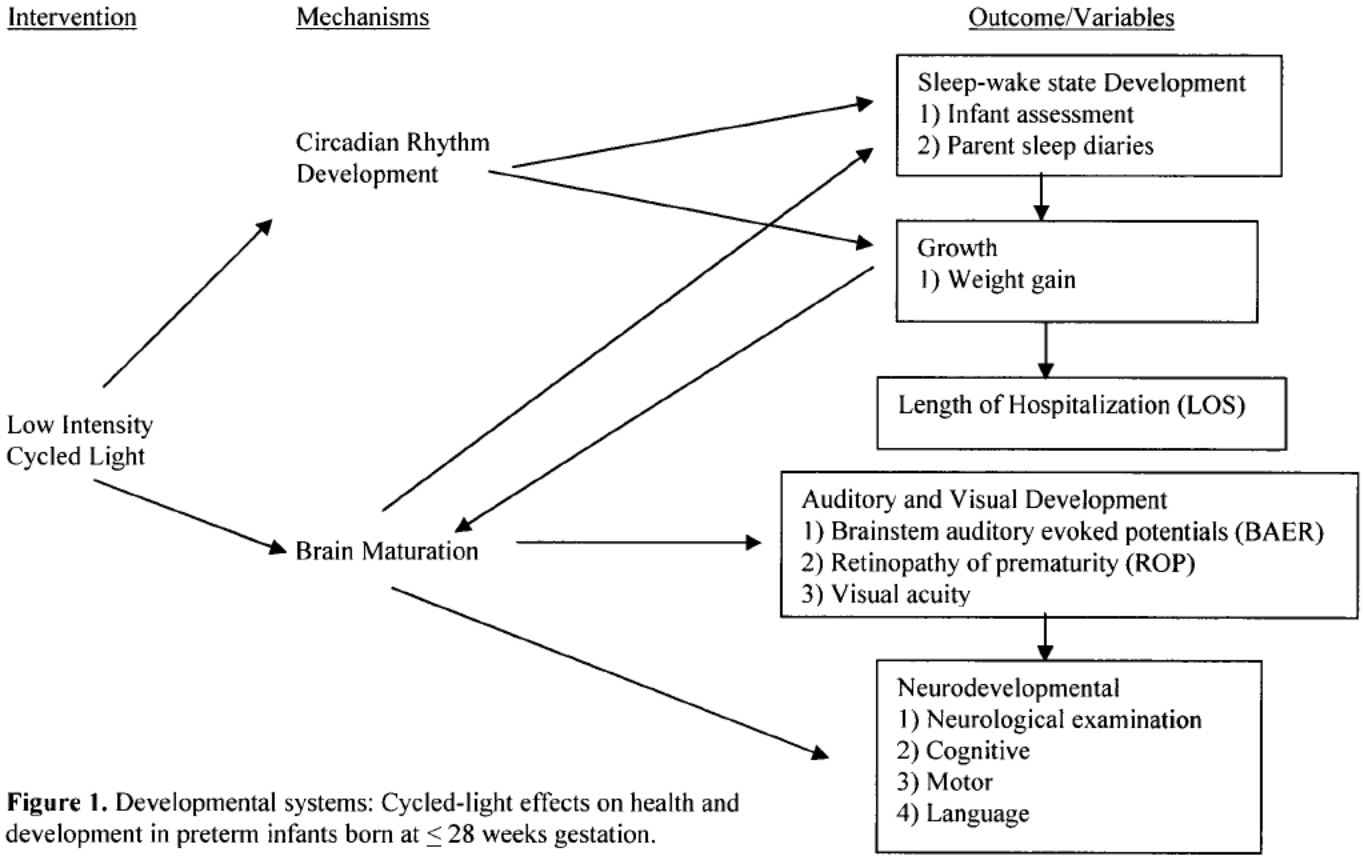

Figure 1. Developmental systems: Cycled-light effects on health and development in preterm infants born at ≤ 28 weeks gestation.

In addition to promoting circadian rhythms, early cycled light may alter neuronal patterning because it is an earlier than expected light stimulus (Lickliter, 2000a; 2000b). Little is known about the effects of earlier than expected light stimulation on human preterm development (Brandon el al., 2002; Fielder & Moseley, 2000; Tsuneishi & Casaer, 2000), but animal research has demonstrated that early sensory stimulation may facilitate, hinder, or leave developmental outcomes unchanged, depending upon the timing of the stimulation and the outcome observed (Lickliter, 2000a; 2000b). It has been suggested that a poorly timed stimulus may be worse than an early or late stimulus (Gottlieb, 1997; Lickliter, 2000a; 2000b) and preliminary study by the principal investigator (Brandon, 2000; Brandon et al., 2002, see Appendix A) suggests that initiation of cycled light at 32 weeks PCA may place preterm infants at more risk for delayed auditory maturation than initiation of cycled light earlier (at 28 weeks PCA) or later (at 36 weeks PCA). Since infants in the proposed study will be receiving cycled light earlier (28 weeks) and later (36 weeks PCA), auditory development is not expected to be affected because the auditory system will not be competing with the initiation of cycled light stimulation at what appears to be a vulnerable point for auditory development (32 weeks PCA).

Circadian rhythm development and brain maturation should facilitate sleep-wake state development (Scher, 1998; Shimada et al., 1999). Preterm infant sleep-wake states demonstrate predictable developmental patterns related to brain maturation in constant light environments (Holditch-Davis et al., 1998b; Scher,

1998), but are more organized, with longer sleep bouts, in a cycled-light environment (Blackburn & Patterson, 1991; Mann et al., 1986) than in a constant-light environment. More organized sleep (Hobson, 1993; Mann et al., 1986; Miller et al., 1995) and more time in sleep (Holditch-Davis et al., 1995) result in better growth. It is unclear how sleep may be affected by near darkness because the majority of the studies examining the development of sleep in preterm infants were conducted in constant bright-light conditions (e.g., Ardura et al., 1995; Holditch-Davis & Edwards, 1998a; Ingersoll & Thoman, 1999). However, continuous near darkness is known to be disruptive to sleep in adults with intact biological clocks (Moore-Ede et al., 1982); therefore, it is hypothesized that preterm infants may be served best by cycled light.

Preterm infants are expected to grow faster in cycled light because secretion of digestive enzymes, a function of circadian rhythm activity, is promoted by cycled light (Moore-Ede et al., 1983; Rivkees, 1997; Scanlon, 1992). Circadian hormones and digestive enzymes may be increased in cycled light environments even in the absence of observable circadian behaviors (e.g., activity patterns) in the infant (Rivkees, 1997). Preterm infants receiving early cycled light (28 weeks PCA) are expected to gain more weight than infants receiving late cycled light (36 weeks PCA) because they will receive cycled light when the retina and SCN are functional (Hao & Rivkees, 1999; Rivkees et al., 1997), and they will not be exposed to the potential stress of very early light exposure (at < 28 weeks gestation). It is hypothesized that when the outcome variables growth and sleep are considered, preterm infants who experience cycled light at the most appropriate time will have better weight gain and brain maturation, leading to more physiologic stability and decreased LOS. **Brain maturation in turn can directly influence auditory, visual, and neurodevelopmental outcomes (Black, 1998; Brandon et al., 2002; Scherjon et al., 2000; Volpe, 1998), and auditory and visual development can also alter neurodevelopmental outcomes (e.g., Cherkes-Julkowski, 1998; Gottlieb et al., 1989; Honeycutt & Lickliter, 2000a; Marshall-Baker et al., 1998; Morris et al., 1999; Sleigh & Lickliter, 1997, 1998; Waber & McCormick, 1995).**

Circadian rhythm stimulation is interrupted and light stimulation occurs earlier than normal for preterm infants, possibly resulting in alterations in the development of neurons and their connections (Black, 1998; Greenough et al., 1987). It is hypothesized that infants exposed to cycled light at 28 weeks PCA will have better neurodevelopmental outcomes because these infants will receive cycled light when the brain has established a full complement of neurons, migration and differentiation are beginning, and the visual sensory system appears capable of handling the stimulation (Dobbing, 1974; Dubowitz et al., 1980; Isenberg, 1994).

Early cycled light may also affect the development of ROP. While the causes of ROP are multifaceted and unclear (Phelps, 1995), Brandon et al. (2002) found a trend toward earlier development of ROP in infants who received late cycled light (36 weeks PCA), suggesting that light may facilitate retinal maturation and alter the developmental path for the visual system (Brandon et al., 2002). However, since earlier development of ROP is not necessarily related to more severe ROP, it is unclear whether earlier ROP affects long-term visual and neurodevelopmental outcomes.

In current practice, preterm infants often must adjust to a continuously bright environment when they are sickest and then make a transition back to a dim or cycled-light environment when they are stable. The environment and circumstances of a preterm infant preclude the elimination of all light, but previous research has demonstrated clear disadvantages of constant light, and the PI's preliminary study (Brandon 2000; Brandon et al., 2002) suggests disadvantages to prolonged near darkness. Therefore it is important to determine when the introduction of cycled light is most appropriate.

C. PRELIMINARY STUDIES

The principal investigator has had significant research experience, as both a principal investigator and co-investigator, including subject recruitment, project management, data collection, analysis and interpretation, and manuscript preparation. As co-investigator on Dr. Holditch-Davis's "Sleep wake states in preterms: Relation to outcome at three years" (National Center for Nursing Research, NIH, FIRST Award,

1987-1990; **Brandon et al., 1999; Huber, Holditch-Davis, & Brandon, 1993**), Dr. Brandon gained valuable experience in management issues related to longitudinal research. She continued her longitudinal research in her dissertation study (F-31 NINR-NIH # NR07180-02; **Brandon et al., 2002**). Dr. Brandon also has had extensive clinical experience in the care of high-risk infants and infants with developmental disabilities. The team of investigators for the proposed study also includes Freedman, a pediatric ophthalmologist who has done extensive research on ROP, and Goldstein, a neonatologist, and Gustafeson, a child psychologist, both of whom have done extensive research on preterm developmental outcomes. Landerman, the statistician, has extensive experience in the methods and statistical techniques of longitudinal research. The consultants round out the research team with expertise in developmental systems theory (Gottlieb), circadian rhythm development (Rivkees), and sleep-wake states (Holditch-Davis).

The proposed study builds upon the principal investigator's initial study of the effects of light on preterm infants (F-31 NINR-NIH # NR07180-02). That study used a longitudinal randomized experimental design to evaluate the timing and short-term effects of cycled light and continuous near darkness on the health and development of preterm infants born at < 31 weeks gestation (Brandon, 2000; **Brandon et al., 2002**). Health outcomes examined included weight gain, ventilator days, hospital length-of-stay (LOS), auditory functioning, and development of retinopathy of prematurity (ROP). Developmental outcomes included sleep-wake state development and neurobehavioral development.

Setting. The research settings were the intensive care nursery (ICN) and transitional care nursery (TCN) at Duke University Medical Center and the special care nursery (SCN) at Durham Regional Medical Center. Duke is a regional perinatal center that receives referrals of both high-risk maternity patients and acutely ill neonates. Durham Regional (a member of the Duke University Health System) is a local hospital that cares for high-risk infants with less acute needs. The ICN was a 24-bed unit for critically ill neonates; and the TCN and SCN are both 12-bed units for stable preterm infants. The SCN is the primary Level II referral nursery for Duke. All of the units have the same medical staff, and the same nursing staff cares for infants in the ICN and TCN. All recruitment of patients took place in the Duke Intensive Care Nursery, with follow-up of patients in both the TCN and SCN Level II units. None of the units were exposed to natural light.

Subjects. Seventy-three infants born at <31 weeks gestation were enrolled over 14 months; 11 infants were dropped from the analyses because they either died (8) or were transferred to a non-study facility (3) before sufficient outcome data could be collected. The final sample included 62 infants. Infants with known anomalies associated with neurological or visual problems (e.g., congenital glaucoma, Down Syndrome) were excluded from participation. Only one infant met the exclusion criteria during study enrollment. Multiple births were included, but each set of multiples was randomized to the same intervention group to avoid confusion for the family. Ten pairs of twins were enrolled, with seven pairs included in data analysis. Three pairs had one twin die prior to the collection of adequate outcome data; therefore only the surviving twin was included in the analyses. The final study sample of 62 had a minimum statistical power of 93% for testing 2% differences, using an alpha level of .05 and an average intervention period of 6 weeks. There were no differences in attrition rates between males and females or whites and non-whites.

Intervention Groups. Neonates were assigned randomly to one of three light intervention groups: 1) cycled light at 32 weeks PCA; 2) cycled light from birth; or 3) cycled light at 36 weeks PCA. The group receiving cycled light at 32 weeks was expected to have more positive health and developmental outcomes than either the group receiving cycled light from birth or the group receiving cycled light at 36 weeks PCA, because these preterm infants would be exposed to light at what appeared to be a developmentally appropriate time. Light was provided with Philips Cool White fluorescent lamps measured as illuminance (lux). Each lamp emitted 5.5% as UVA light and 94.5% as visible light. Filters over the lamps filtered out UVA light; only visible light reached the infant. Infants from the three groups were cared for in the same rooms; therefore other environmental influences were similar. The light was controlled for individual study

infants according to the study protocol regardless of group assignment (see Appendix B for intervention protocol); therefore infants in different groups could be cared for in the same room.

When infants were in near darkness, they received 5-10 lux throughout the day except from 0630-0730 and 1830-1930, when lighting levels varied based on change of shift nursing care needs. Near darkness (5-10 lux) was provided by using incubator (totally covered or with the front flap back) and bassinet covers during the day hours (0730-1830) and either dimming the room light or using covers during the night hours (1730-0630) (see Appendix B). Nurses giving care during times of near darkness (5-10 lux) continued safely with the front flap back and the use of pen lights for areas requiring more intense observation (e.g., intravenous catheter sites). The study provided each of the care nurses with their personal penlight to ensure availability and increase intervention compliance. The covers were lined with black material to maximize light blocking ability. Cycled light was provided in an 11-hour-on, 11-hour-off pattern. Daylight (200-225 lux) was provided with the incubator cover folded on top of the incubator, allowing light in from four sides; or the bassinet cover was kept off during day hours (0730-1830). The hours between 0630 and 0730 and 1830 and 1930 were transition hours in which lighting levels varied based on change of shift nursing care needs. The transition hours were the same for all intervention groups since intervention protocols that could be reasonably replicated were felt to be important for use of findings in other NICUs.

Group status was maintained during lighting for medical procedures by protecting the eyes with eye pads when possible. However, unavoidable breaks in the intervention protocol, such as operative procedures, did occur. These breaks were monitored and did not significantly differ among the groups. In addition, all infants were exposed to unavoidable retinal light stimulation through routinely scheduled ophthalmologic exams at 4 to 6 weeks of age and every 1 to 2 weeks thereafter.

The standard of care in the ICN is to place infants in an incubator as soon as possible; therefore, all study infants were in incubators within 6 hours of age. The type of bed and lighting used with an infant were documented as part of standard nursing computerized bedside charting. Documentation guidelines in the ICN and TCN required the care nurse to document the infant's bed and lighting status at the beginning of every shift and whenever the status changed. The SCN did not document the bed or lighting used, but bi-weekly checks of both day and nighttime intervention status revealed excellent protocol compliance (94%). There was 92% compliance with the protocol in the ICN and TCN. Non-compliance was defined as an infant's cover being placed in the wrong position for the time of day and the intervention group assignment. Compliance with the intervention protocol was achieved through staff education on the purpose of the research and the methods for carrying out the intervention protocol. Incubator and bassinet covers had been in use prior to initiation of the study, but there was no specific standard of care regarding lighting in place. Since the investigator was also the clinical nurse specialist for the nursery, she was physically present in the nursery, and had the respect and confidence of the nursing and medical staff, and the study was well received and supported. As new nursing and medical staff were hired, the investigator educated them to the study procedures. Compliance with the intervention protocols was similar across the three intervention groups and over time.

Light and near-darkness measures were taken weekly at each study infant's bedside to monitor any unknown environmental differences that might have occurred. The day of the week sampled rotated weekly such that each day was sampled over a 7-week period. **The mean lux measures remained in the ranges established for near darkness (5-10 lux) and light (200-225 lux) throughout the study.**

Outcome Variables Outcome measures included health indices (weight gain, hospital and ventilator days, hearing, and ophthalmologic examinations of retinal development), developmental status (sleep-wake states, neurobehavioral exam) (Korner et al., 1988), and day-night differences in mean heart rate.

Weight gain. Infants were weighed daily by their care nurse and weekly weight gains were calculated for the analysis. The scales were routinely calibrated by the medical engineering staff, and none of the unit's scales experienced any significant drift during the study period ($\pm$ 0.01%).

Length of hospitalization and number of ventilator days. The number of intensive care and hospital days and the number of days on the ventilator were counted to evaluate the intervention effects. The natural logarithms of hospital and ventilator days were used for analysis because the variables were highly skewed.

Hearing (brainstem auditory evoked response, BAER). The BAER was conducted by the ICN audiologist as close to discharge as possible so that infants were no longer requiring antibiotic therapy or at risk for other conditions that might affect hearing. Infants were tested using the Algo BAER instrument. Results were categorized as pass (35 dcB, or no more than a mild hearing loss) or fail (a hearing loss could not be ruled out and further audiologic testing was to be conducted following discharge).

Retinopthy of prematurity. Ophthalmological exams were conducted weekly, bi-weekly, or monthly beginning at 1 month of age (6 weeks of age for infants born at <25 weeks-gestation) until the infant had mature retina, was discharged, or ROP disease had resolved. The frequency of exams was determined by the neonatal ophthalmologist based on the absence of disease, immature retina, or the severity of ROP disease. The International Classification of ROP was utilized to categorize disease: Stage 1, demarcation line; Stage 2, ridge; Stage 3, ridge with extraretinal fibrovascular proliferation; Stage 4, partial retinal detachment; Stage 5, total retinal detachment.

Sleep-wake states. Developmental patterns and day-night differences by intervention group were measured at 32 and 36 weeks PCA. The 32-week measure was important because it was the time point when the group began receiving cycled light. Infants were videotaped for a 2-hour inter-feeding period to capture at least one full sleep cycle. The videotaping was done both at night (1800-2400) and during the day (1000-1500) to assess for development of day-night differences.

The sleep-wake state tapes for each infant were transferred to a scoring tape, with infants mixed by intervention group to eliminate possible cues regarding group assignment. Occurrences of four sleeping and waking states (awake, sleep-wake transition, active sleep, and quiet sleep) were coded using the observation system developed by Holditch-Davis (1990a). The investigator and two research assistants were trained by Holditch-Davis to code sleep-wake data. They were unaware of the infants' intervention group assignment. Percent exact agreement on occurrences with Holditch-Davis and the investigator were: awake—94%, sleep-wake transition—92%, active sleep—91%, quiet sleep—88%. Inter-rater reliabilities (percent exact agreement on occurrences) between the investigator and research assistants were determined at the beginning of the study and on every 10 subjects thereafter. The average inter-rater reliabilities between the study investigator and the first research assistant were awake—90%, sleep-wake transition—92%, active sleep—88%, quiet sleep—86%; and between the study investigator and the second research assistant, awake—93%, transitions—88%, active sleep—89%, quiet sleep—87%.

Neurobehavioral exam. Neurobehavioral assessment of the preterm infant (NAPI) was used to assess behavioral organization at 32 and 36 weeks PCA. Items on this test assess motor development and vigor, range of passive movements, inanimate and animate orientation to visual and auditory stimuli, and behavioral state. Seven standardized cluster scores including scarf sign, motor development and vigor, popliteal angle, alertness and orientation, irritability, cry quality, and percent asleep ratings are calculated from the individual items. Normative values are available between 32 and 37 weeks post-conceptional age. All exams were conducted between 1200 and 1600 during an inter-feeding interval.

Procedures. Families were approached for consent antenatally or as soon as they were available for informed consent. The investigator obtained informed consent on all infants. Fifty percent of the consents were obtained antenatally, and 50% postpartum. There were four refusals to participate and two withdrawals secondary to group assignment. Infants were enrolled within 48 hours of admission into the intensive care nursery and, with the aid of a computer generated random list, assigned to one of three intervention groups. Randomization was stratified based on birth weight < 1000 grams and > 1000 grams. Intervention was initiated following group assignment and continued until discharge. Each bedside had an intervention card for near darkness or cycled light to inform the care nurse of the intervention assignment for

each infant. When infants received cycled light at 32 and 36 weeks PCA, respectively, the bedside card was changed to reflect the switch to cycled light.

Baseline descriptive and illness data were obtained from the medical record when the infant was enrolled in the study and weekly thereafter. Two neonatal ophthalmologists conducted ophthalmological examinations.

The investigator conducted the 32- and 36-week neurobehavioral examinations because a trained research assistant blind to study group assignment was not available. The exam was conducted in a quiet room using standardized procedures. Sleep-wake state assessments were done during the same week, but not on the same day. The timing of the sleep-wake assessment was coordinated with parents and health care providers, who were asked not to disturb the infant during the 2-hour period (except for medical emergencies). The nursery audiologist who was blind to group assignment, obtained the brainstem audiological evoked responses (BAER) the week prior to discharge. The chart was reviewed at discharge for collection of all final data including length of hospitalization.

Data analysis. A mixed general linear model (Vollmer et al., 1988) was used to analyze weight gain over time, and the development of sleep-wake states and neurobehavioral development. Length of hospitalization (LOS) and ventilator days were evaluated using analysis of covariance (Maxwell & Delaney, 1990). Auditory functioning (BAER) was analyzed using Fisher's Exact test and chi square procedures (Hays, 1988). General estimating equations (Zeger et al., 1988) were used to evaluate differences in ROP development.

Results and discussion. Infants receiving cycled light from birth and at 32 weeks PCA had significantly greater weight gain over time and showed a trend towards fewer ventilator days and LOS, though these differences did not reach statistical significance. It is possible that the sample size was inadequate to detect differences in LOS and ventilator days. Mean weekly weight gains were as follows: cycled light at 32 weeks PCA, 120 grams; cycled light from birth, 117 grams; and cycled light at 36 weeks PCA, 95 grams. There was significant weight gain over time for all groups, $F(1/59 = 54.9; p < .0001)$; however, there were significant differences between the three groups in the trajectory of weight gain over time (PCA). Patterns of weight gain before and after 32 weeks PCA differed significantly, $F(1,569) = 4.82$; $p = 0.03$, and there was a significant interactive effect between the 32-week time point and the linear trend, $F\ 1/569 = -3.45$; $p = 0.001$. In infants receiving cycled light at birth, and at 32 weeks PCA, growth accelerated significantly earlier than in the group receiving cycled light at 36 weeks PCA, $F(1/569) = 2.55$; $p = 0.01$ and $t(1/569) = 2.04$; $p = 0.04$, respectively) (Brandon et al., 2002, Appendix A).

Previous authors have suggested that early light exposure may be related to the development of ROP (Glass et al., 1985), but in this study infants exposed to prolonged near darkness developed ROP earlier than infants receiving cycled light from birth. That is, the group receiving cycled light at 36 weeks PCA developed ROP earlier ($Z = -1.69$; $p = .09$) than the group receiving cycled light from birth with a **mean gestational age 28 weeks (Brandon et al., 2002, Appendix A).** However, the maximum severity of ROP, as assessed by Fisher's Exact test, did not differ significantly among the three groups. **Thus earlier development of ROP may not have any clinical significance or be related to poorer visual outcomes; further research is needed to evaluate the long-term effects of light on ROP and visual outcomes.**

During hospitalization, infants receiving cycled light at 32 weeks PCA experienced significantly more auditory failures, as measured by brainstem auditory evoked potentials, than infants receiving cycled light at 36 weeks PCA. There was no significant difference between infants receiving cycled light at birth **(mean gestational age 28 weeks)** and at 36 weeks PCA. **This was an unexpected finding, and it suggests that initial light exposure at 32 weeks PCA may affect auditory maturation, though earlier exposure does not have the same effect. On BAER examinations repeated after discharge, there were no significant differences between infants receiving cycled light at 32 and 36 weeks PCA. Additional study is necessary, however, to determine whether light exposure alters other aspects of development.**

There were no significant group differences in short-term neurobehavioral or sleep-wake state development outcomes, but like LOS and number of ventilator days, the power may have been too low for these variables. In addition, since there were only two sleep-wake state data points, developmental patterns were difficult to ascertain.

Following the analysis of primary outcome variables, each variable was evaluated to determine if light effects differed as a function of race or gender. There were no differences on any of the outcomes for race or gender.

While most NICUs across the country modify the light environment in some fashion, a national standard of care for environmental light does not exist. These preliminary findings suggest that there may be an advantage to cycled light over near darkness, depending upon when cycled light is initiated. However, the small sample size and use of only two sleep-wake data points limited evaluation of LOS, number of ventilator days, and sleep-wake outcomes. **In addition, the benefits of prolonged near darkness that have led many nurseries to adopt near darkness as the standard of care have centered on long-term neurodevelopmental outcomes. Thus while early initiation of cycled light appeared to be more beneficial for short-term outcomes than late initiation (36 weeks PCA), long-term outcomes must be evaluated to make sure these benefits persist.**

Lack of weight gain differences between the infants receiving cycled light from birth and at 32 weeks PCA may be explained by the fact that most of the infants receiving cycled light from birth were $\geq$ 28 weeks gestation at birth. This fact, along with the unexpected finding of more auditory acuity failures in infants receiving cycled light after 32 weeks PCA and a trend towards slower development of ROP in infants receiving cycled light from birth, suggests that infants may benefit most from cycled light at some point between birth and 32 weeks PCA. The literature suggests that 28 weeks PCA may be an appropriate time point, but this needs to be evaluated. Further study should also include at least three sleep-wake state assessment points and surveillance of environmental noise. Since infants in this study were cared for in the same rooms, environmental noise should have been similar among the groups. However, since noise can have a major influence on preterm health and development (Morris et al., 2000), future research must include noise surveillance measures.

Determining the most appropriate timing for the initiation of cycled light is a major component of the research that must be done to ensure that the NICU light environment has positive effects on the health and development of preterm infants. Additional studies will need to evaluate the interactive effects of cycled light and environmental events such as feeding frequency on the development of circadian rhythms, and on infants' health and development. In addition, the effects of cycled light in combination with other environmental stimulation, such as auditory stimulation, should be explored, since multi-modal stimulation has the potential to affect short- and long-term developmental outcomes (Sleigh et al., 1998).

D. RESEARCH METHODS

In the proposed study, a longitudinal randomized experimental design will be used to examine the most appropriate timing for replacing continuous near darkness with cycled light in preterm infants born at $\leq$ 28 weeks gestation. The study will examine the effects of early (28 weeks) and late (36 weeks) cycled-light stimulation on short- and long-term health and developmental outcomes, including sleep-wake state development, weight gain during hospitalization, lung maturation, length of hospitalization (LOS), auditory and visual development, and neurodevelopmental outcomes (see Table 1 on page).

Settings. The clinical settings will be the intensive care nursery (ICN) and transitional care nursery (TCN) at Duke University Medical Center and the special care nursery (SCN) at Durham Regional Medical Center (described in Preliminary Studies). All infants will be recruited from the ICN, with the intervention continuing in the TCN and SCN. Following renovation, the ICN is now a 39-bed unit for critically ill neonates; the TCN, a 12-bed unit, and the SCN, a 12-bed unit, are for stable growing preterm infants. The TCN is exposed to natural light, but has electronically operated blinds to control light intensity and

wavelength exposure during daylight hours. All nurseries have individual bed space lighting to permit control of individual subjects' light environment. **Clustered care, nap times, position boundaries and kangaroo care are standard care in each of the study nurseries. However, data will be collected on the use of these care strategies to ensure similarities across groups. If differences exist, the strategies will be added as covariates to the outcome analyses that they may affect (e.g., nap times and weight gain).**

Follow-up assessments after discharge will be conducted in the Special Infant Care Follow-up Clinic (SICC) and Ophthalmology Clinic of the Duke McGovern-Davidson Children's Health Center (CHC). The CHC is a new facility that houses the Duke outpatient pediatric specialty clinics including follow-up for preterm infants. Preterm infants born $\leq$ 28 weeks gestation are routinely followed in the SICC clinic at 9 and 18 months corrected age (CA) and in the ophthalmology clinic until at least 14 months corrected age. The follow-up rates for the two clinics are 85% to 90%. **Duke University Medical Center nurseries and follow-up programs are members of the NICHD Neonatal Network.**

Subjects. One hundred and forty infants born at $\leq$ 28 weeks gestation will be enrolled over a period of 20 months. All recruitment will take place at Duke. Current statistics suggest that Duke's nurseries will admit approximately 320 eligible infants during the enrollment period. Inclusion criteria include: < 48 hours of age or > 48 hours (up to 7 days) but still receiving photo-therapy (eyes are covered with eye pads), approval of the infant's physician, 23-28 weeks gestational age (assessed according to **Ballard et al., 1991, standardized for infants < 28 weeks gestation**), parental consent, cared for in incubator or bassinet, English speaking parents, and no history of known anomalies associated with neurological or visual problems (e.g., congenital glaucoma, Down Syndrome). Multiple births will be included, but each set of multiples will be randomized to the same intervention group to provide consistency for families. If more than one multiple survives until discharge, one infant will be randomly selected to be used in data analyses. Families will receive $30.00 to pay for gas, parking, and food for each hospital visit for all surviving multiples regardless of study participation. Based on the success of minority recruitment in the investigator's original study (68% non-white and 50% female) and current ICN admission data, infants in the proposed study should be at least 60% non-white and 45% female. The study will hire at least one minority research assistant to aid in subject recruitment. With the use of only one infant from multiples, deaths, withdrawals, and loss to follow-up, it is anticipated that 100 of the 140 enrolled infants will be available for analysis.

Sample size determination. The total required sample size, 100 infants (50 per group), was determined by considering weight gain, LOS, and key developmental hypotheses. Power determinations were based on repeated measures techniques because power analyses are not available for mixed model statistics. Weight gain is very important because it has the potential to affect other health and developmental outcomes. Using power estimation methodology developed by Muller and Barton (1989), a total sample size of 100 will have power equal to 0.93 for detecting 2% differences in mean weekly weight gain (Brandon, 2002), assuming a significance level of 0.05, a minimum intervention period of 8 weeks (28-36 weeks PCA), and discharge home after 36 weeks PCA. **Power for LOS was estimated based on data from the PI's preliminary study (Brandon et al., 2002). The LOS model included intervention group, birth weight, time to full calories, and two significant interaction terms (intervention by birth weight, birth weight by time to full calories). The power to detect differences in LOS with this model was 0.96 with a significance level of 0.01.**

Cognitive, motor, and language development are the primary long-term outcomes being investigated. Power determination for the mental and motor scales of the Bayley Scales of Infant Development Second Edition (BSDI-II) and the receptive and expressive scales of the Receptive-Expressive Emergent Language Scale REEL were determined using data from Vohr et al. (2000) and Mahalanobis distance (Stevens, 1992, p.180) for multivariate analysis of variance (MANOVA). Let μ_{11} be the mean motor score for infants in the early cycled light group, μ_{21} be the mean motor score for infants in the late cycled light group, μ_{12} be the mean cognitive score for infants in the early cycled light group, μ_{22} the mean

cognitive score for infants in the late cycled light group, μ_{13} the mean expressive language score for infants in the early cycled light group, μ_{23} the mean expressive language score for infants in the late cycled light group, μ_{14} the mean receptive language score for infants in the early cycled light group, and μ_{24} the mean receptive language score for infants in the late cycled light group. Define $\boldsymbol{\mu}_1 = \begin{bmatrix} \mu_{11} & \mu_{12} & \mu_{13} & \mu_{14} \end{bmatrix}^T$ and $\boldsymbol{\mu}_2 = \begin{bmatrix} \mu_{21} & \mu_{22} & \mu_{23} & \mu_{24} \end{bmatrix}^T$.

Multivariate analysis of variance will have power equal to 0.90 (Stevens, 1992, p.180) $H_o : \boldsymbol{\mu}_1 = \boldsymbol{\mu}_2$ versus $H_o : \boldsymbol{\mu}_1 \neq \boldsymbol{\mu}_2$, assuming 1) a sample size of 50 in both groups, 2) a minimum Mahalanobis distance $(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)^T \boldsymbol{\Sigma}^{-1} (\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)$ equal to 0.64, and 3) equal population covariance matrices. Using motor and cognitive data from Vohr et al. (2000), the estimated Mahalanobis distance was 11.3, suggesting the minimum effect size requirement of 0.64 used for the power calculation will be satisfied.

Follow-up analyses are anticipated. Analysis of variance will have power equal to 0.80 to test $H_o : \mu_{11} = \mu_{21}$ versus $H_1 : \mu_{11} > \mu_{21}$ (motor differences), assuming a sample size of 50 in both the early and late cycled light groups, a minimum mean difference of 10.0, common standard deviation of 18.3 (Vohr et al., 2000), and a level of significance of 0.05. Analysis of variance will have power equal to 0.89 to test $H_o : \mu_{12} = \mu_{22}$ versus $H_1 : \mu_{12} > \mu_{22}$ (cognitive), assuming a sample size of 50 in both groups, a minimum mean difference of 10.0, common standard deviation of 17.2 (Vohr et al., 2000), and a level of significance of 0.05. No pilot data exist for testing either $H_o : \mu_{13} = \mu_{23}$ versus $H_1 : \mu_{13} > \mu_{23}$ or $H_o : \mu_{14} = \mu_{24}$ versus $H_1 : \mu_{14} > \mu_{24}$; however, we anticipate effect sizes of comparable magnitude. This will result in corresponding power, ranging from 0.80 to 0.93, and sample size requirements of 50 subjects per intervention group.

Hence, the total required sample size for this study is $N = (2 \text{ intervention groups}) \left(\frac{50 \text{ subjects}}{\text{intervention group}} \right) = 100$ subjects. The initial enrollment of 140 infants will permit 29% attrition, and still allow for adequate power for testing key hypotheses.

Intervention Groups. **Neonates will be stratified according to birth weight ≤ 750 grams and > 750 grams (standard break point for extremely low birth weight infants) to help ensure that the intervention groups are equal on this important covariate. Birth weight will also be used as a covariate in sleep-wake states, visual acuity, and weight gain to control for its effects on state and visual development and growth.** The groups will be randomly assigned with the aid of a computer generated list to one of two intervention groups: 1) early cycled light (28 weeks) (0-5 weeks of near darkness, 12-16 weeks of cycled light), or 2) late cycled light (36 weeks PCA) (8-13 weeks of near darkness, 4-8 weeks of cycled light). **The intervention length for the both early and late cycled light should be long enough to entrain circadian rhythms (12-16 weeks, early cycled light; 4-8 weeks, late cycled light) (McGraw et al., 1999). Currently, both of these lighting methods are used at Duke and Durham Regional, based upon staff nurse evaluation rather than any systematic care protocol. Consequently, infants not participating in the study will not have consistent exposure to either near darkness or cycled light from day to day.** Light will be measured as illuminance (lux), a measure of the reflective abilities of a surface. For example, a white wall illuminates more than a black wall regardless of the amount of light that is shining (ISENA Survey, 1994). Current research has used illuminance (primarily as lux) when studying the effects of light (e.g., Lotas, 1992; Mann et al., 1986; Miller et al., 1995).

Light in the ICN and SCN will be provided with **Philips and GE Cool White fluorescent lamps. Each lamp emits 5.5% as UVA light and 94.5% as visible light. Filters over the lamps are designed to filter out UVA light; thus only visible light wavelengths should reach the infant. Light in the TCN will be provided by both Philips and GE Cool White fluorescent lamps and natural light. Filters will be**

added over the windows in the TCN to filter out the UVA light in natural light. Window shades will also permit control of natural light as necessary (see below).

Continuous near darkness will be provided as 5-20 lux throughout the day except from 0630-0730 and 1830-1930, when lighting levels will vary based on nursing care needs at the change of shift. Near-darkness (5-20 lux) will be provided by using incubator (totally covered or with the front flap back) and bassinet covers and dimming individual bedside light during the day (0730-1830) and night hours (1730-0630). The incubator and bassinet covers are lined with black material to maximize light blocking ability. The range of 5-20 lux of light can be maintained regardless of the position of the incubator cover (Brandon et al., 2002), and provides similar illumination. Illuminance at both 5 and 20 lux is sufficiently dim to make it difficult to evaluate skin color and catheter sites without pen light assistance. Nurse caregiving during times of near darkness can safely continue with the front flap back and the use of pen lights for areas requiring more intensive observation (e.g., peripheral intravenous catheter sites). The study will provide each care nurse with his or her personal penlight to ensure availability and increase intervention compliance.

Cycled light will be provided in an 11-hour-on, 11-hour-off pattern. Daylight **(200-300 lux)** will be provided with the incubator cover folded on top of the incubator allowing light in from four sides, or with the bassinet cover off during day hours (0730-1830). **With the daylight range of 200-300 lux and limited access to natural light, daylight can be ensured for infants in incubators and bassinets. Both 200 and 300 lux of light are sufficiently bright to easily read and assess infant color and catheter sites and are not visibly different to the naked eye. This range of lux light is also sufficient to entrain circadian rhythms (Rivkees, personal communication 2002; Rivkees et al., 1997). In the nursery with natural light, the room lights will be used to maintain the standard light levels. On cloudy days the lux levels in the nursery do not exceed 300 lux, and on sunny days the nursery blinds will be used to block natural light as needed to maintain 300 lux.** Near darkness will be provided as described above during night hours.

The hours between 0630 and 0730 and 1830 and 1930 will be transition hours in which lighting levels will vary based on change of shift nursing care needs. The transition hours will be applied to both intervention groups since protocols that can be reasonably replicated are felt to be important for application of findings to other NICUs. **The Extech light meter will be used to evaluate light measures in all bed spaces in incubators and bassinets and with the protective device in different positions, to ensure ability to maintain near darkness (5-20 lux) and daylight (200-300) (see Appendix B).**

The standard of care in the ICN is to place infants of this gestational age in incubators as soon as possible; therefore, all study infants should be in incubators within 4-6 hours of age. Documentation guidelines in the ICN and TCN require the nurse to document the infant's bed and lighting status at the beginning of every shift and whenever the status changes. The SCN documents bed and lighting use on a paper bedside flow sheet.

Since infants from both intervention groups will be cared for in the same nursery rooms, it is not expected that the noise environment will differ between intervention groups. However, to ensure that noise levels do not differ in the nursery rooms, random 24-hour assessments of noise levels will be conducted weekly in every room caring for study subjects. Noise will be measured using a data logging dosimeter (Noisemeters Inc).

Maintaining intervention integrity. As the clinical nurse specialist for the Duke nurseries and consultant for the DRH nursery, the principal investigator (PI) is well respected by the nursing and medical staff. The nursing staff's familiarity with procedures and high compliance with the intervention protocol in the preliminary study (discussed in the Preliminary studies section) should ensure good compliance with the proposed study. Prior to study initiation, the PI will conduct staff training on the intervention protocol to ensure understanding of the procedures. New nurses hired during the study period will be trained during their first week of orientation. Incubator and bassinet covers and individual bed space lighting will permit

infants in different intervention groups to be cared for side by side without compromising intervention integrity.

Bedside cards designating intervention status (near darkness or cycled light) will be posted at each infant's bedside as a reminder for the care nurse. When the cards are changed to cycled light at 28 and 36 weeks, care nurses will be verbally reminded of the intervention change and will be asked to pass this information on the next care nurse during verbal shift-to-shift report. Random compliance checks with the intervention protocol will be conducted bi-weekly for each study infant. The day and time of the week sampled will be rotated at each sampling period such that each day and shift will be sampled over a 12-week period. Non-compliance will be defined as an infant's incubator or basinett cover being placed in the wrong position, or room lights being incorrect for the time of day based on intervention group assignment. If the infant's intervention status is incorrect during compliance checks, the care nurse will be consulted regarding the need for a break in intervention status and will be reminded of the infant's intervention assignment and the importance of intervention integrity.

As noted earlier, the Extech light meter will be used to evaluate light measures in all bed spaces in incubators and bassinets and with the protective device in different positions to ensure continued ability to maintain near darkness (5-20 lux) and daylight (200-300). Measures for near darkness and cycled light will be taken bi-weekly at each subject's bedside to monitor any unknown environmental differences that may occur. The day of the week sampled will be rotated at each sampling period, and each day will be sampled over a 3 1/2 week period. In addition, lamp use will be monitored to ensure that light wavelengths are not altered during the study.

Descriptive and Covariate Variables. Selected demographic and illness-specific data will be obtained from the medical record when the infant is enrolled in the study and weekly during hospitalization. Illness specific data will be collected again after hospital discharge from the SICC medical record, and will include new diagnoses and re-hospitalizations. The data will be used to describe the sample and monitor potential group differences on variables that have the potential to affect the outcomes of interest. Demographic data will include birth weight, gestational age, gender, race, maternal age, **maternal drug use**, and maternal education. Illness specific data will include 1-minute and 5-minute Apgar scores, intraventricular hemorrhage stage, presencepatent ductus arterious, medication history, infections, **length of photo-therapy**, day of life for the first feeding, length of time to reach growing calories without regression, and severity of illness as measured by the Score of Neonatal Acute Physiology (SNAP-I) (Richardson et al., 1993). **Length of time to reach growing calories without regression** is defined as the number of days until the infant is on growing enteral calories (100cc/kg/day) and remains on growing calories until discharge. **Differences between intervention groups on any of the demographic or illness-specific variables (e.g., chronic lung disease, IVH, maternal drug use, maternal education) will be added to the data analysis as covariates to evaluate any explanatory tendencies.**

The SNAP-I score quantifies severity of illness using a set of routinely obtained laboratory and clinical parameters reflecting the integrity of the body's seven main organ systems. The greater the departure from physiologic norm, the more severe is the illness. The most abnormal value for each item during the 24-hour scoring period is selected for scoring. A score of 0-5 is assigned to each of 26 items, with a range of 0-130 for the entire scale. A score of zero is assigned to items that are normal or have not been assessed during a patient's routine clinical care. This zero assignment assumes that abnormal physiologic status would have prompted laboratory and/or clinical investigation. One point is assigned to an abnormality within a range worthy of concern, but not necessarily requiring treatment. Three points are assigned to items in a range that under most circumstances would cause most physicians to change therapy. Five points are assigned to life threatening abnormalities. For each observation period, the most abnormal value for each item will be abstracted and scored. For some items, derangements on both the high and low end may both be scored (e.g., serum sodium). SNAP-I is the sum of points for all items (see Appendix C-1). **The SNAP-I is highly correlated with therapeutic intensity (use of technology) ($r = .78$, $p < .01$) and in-hospital mortality ($p < .001$) (Mattia &**

deRegnier, 1998). It will be measured at 1, 3, 7, and 14 days of life to describe the groups' severity of illness over time. These measurement points were selected because severity of illness should be most reflective of mortality on day of life 1, ventilation requirements on day of life 3, chronic lung disease on day of life 7 and general chronicity on day 14 (Richardson et al., 1993).

The Home Screening Questionnaire, birth to 3 years (HSQ; see Appendix C-2) (Coons et al., 1981), will be used to evaluate the potential influence of the home environment on weight gain and neurodevelopmental status (neurologic, cognitive, motor, and language outcomes) at 12 and 24 months PCA that could confound the long-term effects of cycled light. **The HSQ will be completed during the SICC visit.** The questions are formulated at the 3rd to 6th grade reading level and can be completed in 15 minutes. The HSQ can be read to parents who do not have a 3rd grade reading level. **The internal consistency coefficient is .74 and test-retest reliability is .82 for children 1-3 years of age (Coons et al., 1981). The HSQ predicted between 81% and 86% (Frankenburg, 1986) of the environments determined to be of concern by the HOME Inventory (Caldwell & Bradley, 1980). The HOME Inventory has been correlated with cognitive abilities ($r = .42$, $P < .01$) (Holditch-Davis et al., 2000).**

Outcome Variables. Outcome measures will include health indices (weight gain, LOS, hearing, development of ROP, visual acuity) and neurodevelopmental status (sleep-wake state development, neurological impairments, and cognitive, language, motor development). Short-term outcomes will be evaluated weekly, at 30, 33, and 36 weeks post-conceptional age (PCA), and at hospital discharge. **Thirty, 33, and 36 weeks PCA were chosen for the sleep measures because this evenly distributes three collection points after the initiation of the intervention, but before the late cycled light group (at 36 weeks) receives cycled light. Three points are necessary to statistically evaluate a developmental pattern. Long-term outcomes will be evaluated at 9 and 18 months corrected age (CA). These time points were chosen because severe developmental problems are usually present by 9 months of age, and milder developmental delays, including language delays, are evident by around 18 moths of age (Vohr et al., 2000; Volpe et al., 1998). In addition, these time points are the typical evaluation points for infants returning to the SICC and are recommended by the NICHD Neonatal Research Network. Table 1 shows the data collection schedule for each outcome measure.**

Table 1: Timing of Outcome Measures Including Repeated Measures

	Hospital Outcomes					Outpatient Outcomes						
Measures	Weekly in hospital	30 wks PCA	33 wks PCA	36 wks PCA	At discharge	4 mos CA[b]	9 mos CA	12 mos CA	14 mos CA	18 mos CA	19 mos CA	24 mos CA
Short-term outcomes												
Sleep-Wake States		X	X	X								
LOS					X							
Hearing (BAER)					X, repeat after d/c with failure							
ROP Exams	X, bi-weekly, monthly							X				
Weight gain	X						X			X		X
Long-term outcomes												
Parent Sleep Diaries						X	X		X		X	X
Visual Acuity								X				X
Neuro Exam							X			X		
Bayley II							X			X		
REEL							X			X		

[a] PCA = post-conceptional age, [b] CA = corrected age [c] d/c discharge home

Weight gain. Infants will be weighed daily by their care nurse during hospitalization, and daily weight will be summed to determine growth in grams per week. Weight will also be obtained during the SICC visits at 9 and 18 months CA. **The multiple data collection points will permit statistical modeling of weight gain over time.** Medical engineering staff routinely calibrate the scales in the nurseries and the SICC using predetermined weights for a < 1% drift.

Length of hospitalization (LOS). Total number of hospital days will be counted to evaluate the potential of early (28 weeks) and late (36 weeks) institution of cycled light to affect illness and hospital costs. A transformation (e.g., natural logarithm) of LOS will be employed for analysis because these variables are typically highly skewed.

Hearing (brainstem auditory evoked response, BAER). The BAER is the gold standard for neonatal auditory assessment (Lary, 1985). It will be conducted by the ICN or SCN audiologist as close to discharge as possible to ensure that infants are not receiving antibiotic therapy or at risk for other conditions that might affect hearing. Screening after discharge is not recommended because it is too difficult to get a 100% return rate and there is already state-mandated screening for all high-risk infants. The BAER will be repeated after discharge for infants with a failure in either ear to determine whether there is hearing loss or whether the earlier results reflected a lack of maturation. All infants will be tested using the Algo brainstem auditory evoked instrument. Results will be categorized as pass (35 dcB, or no more than a mild hearing loss) fail/pass (failed in the hospital, passed repeat), or fail/fail (failed both in the hospital and after discharge).

Retinopthy of prematurity (ROP). Ophthalmological exams will be conducted weekly, bi-weekly, or monthly beginning at 4 weeks of age (6 weeks of age for infants born at ≤ 25 weeks gestation) until the infant has mature retina or ROP disease has resolved. Exam frequency will be determined by the neonatal ophthalmologist, blinded to group assignment, based on the absence of disease, immature retina, or the severity of ROP disease. The International Classification of ROP will be used to categorize disease: Stage 1, demarcation line; Stage 2, ridge; Stage 3, ridge with extraretinal fibrovascular proliferation; Stage 4, partial retinal detachment; Stage 5, total retinal detachment. A final follow-up ROP exam will be conducted at 12 months PCA.

Sleep-wake states. To evaluate the effects of early and late cycled light sleep-wake states during day and night hours will be measured at 30, 33, and 36 weeks PCA utilizing a state-of-the- To evaluate the effects of early and late cycled light art infant sleep recording system. **The three measurement points needed to evaluate sleep-wake state development will be evenly distributed after the initiation of the intervention, but before the late cycled light group (at 36 weeks) receives cycled light.** The occurrence of four sleeping and waking states (awake, sleep-wake transitions, active sleep, quiet sleep) will be coded using respiration patterns, body movements, and rapid eye movements as described by Holditch-Davis (1990a) (see Appendix C-3). These variables have been shown to exhibit reliable individual differences over time for preterm infants (Brandon et al., 1999; Holditch-Davis, 1990a; Holditch-Davis et al., 1998a) and to detect group differences (Holditch-Davis, 1995; Holditch-Davis et al., 1999a; Holditch-Davis et al., 1999b). The infant's respirations and body movements will be recorded using a piezoelectric sensor pad placed under the crib pad, so that respiration regularity and respiratory pauses in each sleep state can be determined. Two electro-oculogram (EOG) probes will record rapid eye movements. Rapid eye movement measurements by EOG are reliable in preterm infants > 28 weeks gestation (Scher, 1998) and correlate well with sleep-wake state variables (Holditch-Davis et al., 1998b). The respirations and EOG signals will be sent to a 4-channel analog recorder using commercially available software (Biopac Waveform Acquisition System). The respiratory pad and EOG signals will be conditioned using an AC/DC preamplifier, which will generate real-time signals to the analog output jack. The conditioned output will be digitized by a 16-bit analog to digital converter, and the signals displayed and stored on a notebook computer at a rate of 20 samples per second. The infant will continue on normal heart and apnea monitors. Respiration recordings will be scored using a computer-assisted scoring program originally used for visual scoring of respiration regularity and apnea (Holditch-Davis, 1990a; Holditch-Davis et al., 1994). Rapid eye movements will be scored as present or

absent during a 10-second window. A spreadsheet containing all marked timer voltages and lapsed time from the beginning of the file will be generated. The respiratory and EOG data files will then be divided into 10-second epochs using the timer spreadsheet as the reference. An interactive macro program will be created to read the timer spreadsheet and assign epoch values for scoring respiratory and state variables. The research assistants completing the computer-assisted scoring will be blinded to intervention group assignment. The accuracy of computer-assisted scored respiratory and state variables will be checked by evaluating agreement, using kappa coefficients, between randomly selected research-assistant-scored records and those scored by Dr. Holditch-Davis, as well as agreement between research assistants on the records scored. The PI has been trained by Holditch-Davis to code sleep-wake data. The verified data file will be transferred as an ASCII file into the Behave program, which converts each variable into a percentage of the assessment period for analysis. Evaluation of four recordings using Holditch-Davis's (1990a) respiratory waveform and direct observation sleep-wake state measure and the PI's measure of respiratory waveform and EOG sleep-wake state measure had percent exact agreement on occurrences: active sleep—85%, quiet sleep—81% awake—66%, sleep-wake transition—70% (Brandon, 2002 unpublished).

Sleep-wake state assessments will begin at 30 weeks PCA to give all infants in the early cycled light group 2 weeks of cycled light before evaluating day-night differences in state. In addition, most infants should be off of assisted ventilation by 30 weeks. If an infant is receiving assisted ventilation at 30 weeks PCA, the measurement will be performed as soon as possible. Two additional measures at 3-week intervals (33 and 36 weeks PCA) will assess developmental patterns over time by intervention group. Three sleep states (active sleep, quiet sleep, transitional sleep) and time awake (see Appendix C-1) will be evaluated for differences between the groups at each measurement point, and for differences in developmental patterns across time. Infants will be assessed during a 2-hour inter-feeding period to capture at least one full sleep cycle. Data will be collected both at night and during the day to assess for development of day-night differences. Day and night recordings will occur in a consistent 4-hour period of time for all infants (1000-1400 for day recordings and 2000-2400 for night recordings). The principal investigator's previous study used the same time frames without encountering scheduling problems.

To ensure that sleep-wake patterns are not affected by hypoxia or other transient medical complications, infants will not be observed when they are on assisted ventilation, experiencing acute medical complications, during medical procedures, or in the recovery period after a procedure. If an assessment is missed because of health problems, the assessment will be rescheduled as soon as the infant recovers. The proposed statistical procedures will adjust for missing observations and mis-timed data points. Also, these procedures should provide adequate control for atypical weeks. Research has confirmed that individual development deviations from the mixed general linear model are relatively unaffected by a single deviant value (Holditch-Davis & Edwards, 1998). Thus, isolated atypical sleep patterns will not greatly affect this index.

Parent sleep diaries. Sleep-wake state patterns after discharge will be assessed using **parent sleep diaries beginning at 4 months CA and continuing every 5 months thereafter. The diaries are timed for every 5 months in order to be close enough together to identify important changes in sleep-wake state development without being so frequent as to be burdensome.** Parents will be asked to record the time their infant goes to sleep and awakens from naps and nighttime sleep for 7 days (see Appendix C-4). Nighttime awakenings will also be recorded. It will take approximately 5 minutes per day to complete the sleep diaries. **Parents will be given $10 for every returned diary to compensate them for the burden of competing the diaries. Parents have been shown to be compliant in completing infant sleep diaries (Thomas, 2001).**

The diary will be reviewed with parents prior to discharge and over the phone the week before each measure is collected, to ensure their understanding of record completion. **Reminder phone calls will be made if diaries are not returned within 2 weeks, allowing parents 1 week to complete and 1 week to return the diaries.** The diary will be analyzed to determine the average percentage of sleep and awake time

per day, regularity in sleeping times from day to day, and variability in the amount of time spent sleeping and awake from day to day. **Parental recordings of infants' sleeping and waking times have been significantly correlated with objective measures of sleep, with day-to-day stability (Sadeh, 1996). Parents accurately report sleep onset (r = 0.88) and sleep duration (r = 0.74) when evaluated against objective measures of sleep derived from activity monitoring (Sadeh, 1996). Also, adults completing sleep diaries have demonstrated acceptable percent agreement with polysomnographic data (kappa = .87). In addition, considerable evidence of the validity of parent sleep diaries has been demonstrated through examination of relationships between data from the diary and other aspects of parent-infant interactions, infant developmental outcomes, maternal stress, and maternal emotional support (Barnard, 1978; Becker et al., 1987; Becker & McGovern, 1985). In one study (Scott & Richards, 1990), amount of infant sleep recorded by mothers on diaries predicted maternal stress.**

Visual acuity. A pediatric ophthalmologist, blinded to group assignment, will perform the visual preferential looking test to assess visual acuity at 12 months CA, because the sequelae from ROP have typically evolved by this point in time (see Appendix C-5). The test establishes the smallest black and white grating (lines) which an infant is able to differentiate from a homogeneous gray non-patterned environment. There are 17 test plates and one blank plate. The test results in age norms in months. **The preferential looking test has been validated with visual evoked potential protocols for infants between 1.5 and 24 months of age and has good test-retest reliability over 1 week, r = .93 (Birch & Salomao, 1998).** It is the only non-invasive quantifiable assessment of visual functioning for infants. The infant is usually tested in a parent's arms, avoiding separation difficulties. The time required for the test varies, depending upon the attention of the infant. Since there are no electrodes or other mechanisms required, if the infant becomes fussy, sleepy, or hungry, the test can be interrupted, the infant comforted or fed, and the test resumed following a short period of rest.

Neurologic examination. The medical director of the Special Infant Care Clinic, blinded to group assignment, will conduct a detailed neurological exam at 9 and 18 months corrected age. The standard pediatric neurologic examination of Amiel-Tison (1974) will evaluate neurological handicaps, including cerebral palsy. Physicians who perform the neurologic examination commonly score children as neurologically normal, suspect, or abnormal based on their qualitative interpretations of a standard neurologic assessment (Vohr, 1999). Abnormalities of tone will be quantified according to functional impairment, using the following scoring system: 0 = normal tone with normal function; 1 = mild abnormality of tone with normal function (e.g., mild truncal or generalized hypotonia, slight tightness at hips or ankles); 2 = mild to moderate abnormality of tone with mild functional impairment (e.g., delayed motor milestones, impaired quality of movement, mild asymmetry of motor function); 3 = moderate to severe abnormality of tone with moderate functional impairment (e.g., not ambulating with assistance, marked asymmetry of motor function); 4 = severe abnormality of tone with severe functional impairment (e.g., not ambulating, unable to use upper extremities purposefully). **At 24 months corrected age, scores of 2, 3, and 4 reliably correspond to diagnoses of mild, moderate, and severe cerebral palsy, respectively (Goldstein et al., 1995).**

Bayley Scales of Infant Development Second Edition (BSID-II,1993). Cognitive and motor measures will be obtained using the BSID-II at 9 and 18 months corrected age. The BSID-II will be administered by the trained SICC child psychologist, who will be blinded to intervention group assignment. The BSID-II yields a Mental Development Index (MDI) and a Psychomotor Development Index (PDI); each scale has a mean score of 100 with a standard deviation of 15 (Bayley, 1993; see Appendix C-6). The MDI measures aspects of infant cognition (including memory, habituation, problem solving, classification, language, and social skills) and visual-fine motor coordination. The PDI measures gross and fine motor skills. **The MDI and PDI have reliabilities of .88 and .84, respectively. The MDI is correlated with the General Cognitive Index of the McCarthy Scales of Children's Abilities (r = .79), and the PDI is correlated with the McCarthy Motor Scale (r = .59) (Bayley, 1993). The MDI is correlated with the Full Scale IQ (r =**

.73), Verbal IQ (r = .73), and Performance IQ (r = .63) on the Wechsler Preschool and Primary Scale of Intelligence-Revised (Bayley, 1993), which is scored only on older children. The 18-month MDI will provide an estimate of cognitive abilities; the 9-month MDI will identify infants with severe cognitive problems. The PDI measures motor abilities that are independent of cognitive abilities.

Receptive-Expressive Emergent Language Scales (REEL). Receptive and expressive language measures will be obtained using the REEL at 12 and 24 months corrected age. The REEL will be administered by the SICC speech and language pathologist, who will be blinded to group assignment. Receptive language refers to the sensory-neural and auditory perceptual processes that are involved in decoding and understanding oral language. Expressive language refers to the processes and skills that are involved in the encoding of meaning into oral language for communicating with others. The REEL yields receptive, expressive and combined language quotients. Scale scores have a mean of 100 and a standard deviation of 16 (Bzoch, 1971; see Appendix C-7). The REEL has demonstrated validity data that is not affected by gender or ethnicity. **Inter-rater reliabilities have ranged from 90% to 100% and tests re-tests (with 3 week intervals) yielded a correlation value of r = .71 (Bzoch, 1971).**

Procedures. Approval of the attending physician will be obtained prior to approaching families for consent. Families will be approached before delivery when mothers are hospitalized for bed rest or as soon as the mother has recovered from delivery and is available for informed consent. The project coordinator, a research assistant or an investigator will explain the study, allow time for questions, have a parent sign the consent form, and give a copy to the parent. The intervention will be initiated following group assignment and continue until the infant is discharged from the hospital. Incubator covers and bassinet covers are currently used in all three study nurseries. The covers will be examined during the bi-weekly routine intervention compliance checks to ensure that they do not have holes.

Baseline descriptive and illness specific data will be obtained from the medical record when the infant is enrolled in the study. The medical record will be reviewed weekly to obtain additional data (e.g., weights). Routine ophthalmological exams will be conducted by a pediatric ophthalmologist and graded according to the standard scoring of retinal development and retinopathy of prematurity (ROP). Hospital exams will be repeated until the retina is mature with no ROP disease, until hospital discharge, or until the disease has regressed. The care nurse will turn over the bedside intervention card before ophthalmological examinations to prevent accidental un-blinding of the ophthalmologist.

At 30, 33, and 36 weeks PCA infants will have their sleep-wake states assessed. These assessments will be conducted between 1000 and 1400 for daytime recordings and between 2000 and 2400 for nighttime recordings. Exact timing of the sleep assessments will be coordinated with parents and health care providers to capture an interval midway between feedings and avoid disruption of parent visitation. Health care providers and parents will be asked not to disturb the infant during the 2-hour period (except for medical emergencies).

The nursery audiologist will obtain brainstem audiological evoked responses (BAER) the week prior to discharge. Data on BAER evaluations repeated after discharge will be collected from the medical record. During the week of discharge, parents will be reminded of the follow-up data to be collected at 9 and 18 months corrected age (CA) during their routine follow-up appointments in the Special Infant Care Clinic (SICC) and the Ophthalmology Clinic. The chart will be reviewed at discharge for collection of all final hospital data including length of hospitalization.

Follow-up neurological and developmental exams will be conducted at 9 and 18 months CA in the SICC, and ophthalmologic testing will be conducted at 12 months CA. The follow-up tests at 9 and 18 months CA are part of routine follow-up for this patient population. Parents will be called 1 week prior to their scheduled appointments to remind them of their visit date and time, clarify any questions they have, and encourage the presence of the mother during the SICC visit. Parents will receive $30.00 to pay for gas, parking, and food for each hospital visit to compensate them for costs incurred by the visit. **All parent interviews including the HSQ and child testing will be conducted in the Children's Health Center.**

Each child's medical record will be reviewed for pertinent data during each clinic visit. Visits will be scheduled at 9 and 18 months CA, but rescheduling in a 2-month window will be permitted for child illness. Parents will also receive sleep diaries in the mail to be completed at 4, 9, 14, 19, and 24 months CA. The sleep diaries and instructions for completion will be mailed to the parents with a return envelope 10 days before the data are to be collected. In addition, phone calls will be made 1 week before data collection to answer any questions parents may have regarding diary completion. **Reminder phone calls will be made if diaries are not returned within 2 weeks, allowing parents 1 week to complete and 1 week to return the diaries. The $10 compensation for completing each diary will be mailed after the diary is returned.**

Attrition reduction strategies. Except for the sleep-wake state assessments during hospitalization and the parent sleep diaries after discharge, all of the outcome measures are standard care for preterm infants born at $\leq$ 28 weeks gestation. Therefore, the study burden should be minimal. In addition, the return rates in the follow-up clinics are excellent (85%-90%). Since the PI is the ICN and TCN's clinical nurse specialist and a member of the health care team, families will have a caregiving relationship with Dr. Brandon. This relationship should help reduce attrition. Phone contact with families will take place every 4 months as parents are reminded and re-educated about sleep diary data collection. In addition, all families will receive infant birthday and holiday cards from the study to maintain contact and keep up-to-date addresses and phone numbers after discharge home.

Statistical analysis Prior to statistical analysis, the SNAP-I, state data, and neurodevelopmental examinations will be scored. Weight gain will be summarized to determine average gains per week. Descriptive statistics will be calculated for all variables. Demographic and illness data from each group will be compared to assess group differences. Variables on which there are significant between-group differences will be entered as covariates in hypothesis testing.

The outcome variables of interest include health indices (average weight gain per week during hospitalization, LOS, hearing, retinopathy of prematurity during hospitalization and at 12 months of age CA, visual acuity at 12 months CA, and weight at 9 and 18 months CA), and developmental status (sleep-wake diaries at 4, 9 14, 19, and 24 months CA and neurological status, and cognitive, language, and motor development at 9 and 18 months CA). The outcome variables represent a mixture of continuous and categorical data. Data analysis plans are discussed below for each hypothesis.

Hypothesis # 1. Infants receiving early cycled light (28 weeks PCA) will have significantly more organized sleep-wake states before and after hospital discharge than infants receiving late cycled light (36 weeks PCA), after covarying the effects of intraventricular hemorrhage, birth weight, caffeine, and length of mechanical ventilation. A mixed general linear model will be used in two separate analyses to evaluate sleep-wake organization using the objective measure of sleep-wake states during hospitalization and the parent sleep diaries following discharge. The mixed general linear model is a flexible statistical framework in which the regression of each subject is represented by its deviation from the group regression (Andrade & Helms, 1986a, 1986b; Fairclough & Helms, 1986; Laird & Ware, 1982; Vollmer et al., 1988). The mixed model has three components: a fixed effects component, a random effects component, and a random error component. Each subject is represented by the sum of the fixed effects component and the random effects components for that subject. Because each subject is represented in the model, the mixed model can accommodate missing and mistimed data without requiring an estimation of missing data. The fixed effects and random error components are analogous to the corresponding components of a standard multiple regression. The random effects component for each subject is the difference between the subject's regression and the total group regression and is a measure of how this subject differs from the population regression, as each subject has his or her own intercept and slope.

The analyses from hospital data will be used to evaluate whether sleep-wake state development exhibits day-night differences over time for each intervention group. In addition, the mixed model will be used to evaluate differences in the amounts and developmental changes in sleep wake states between the two intervention groups. Each sleep-wake state will be regressed over PCA, time of day (day/night), and

intervention group. Intraventricular hemorrhage, birth weight, caffeine, and the log of mechanical ventilation will be used as covariates in the fixed effects component of the model because of their potential to affect state (Brandon et al., 1999; Holditch-Davis, 1990a; Holditch-Davis, 1990b). Caffeine will be a time varying covariate. The intercept, PCA, day-night differences, and intervention group effects will be included in the random effects component to allow each infant to have his or her own individual developmental trajectory. Prior to the analysis, PCA will be "centered" at 28 weeks gestation, such that the 28-week data point is scored as 0 and other ages are scored in weeks above or below 28 weeks.

A model reduction procedure will be employed whereby all variables, including intercept and the linear effects of PCA, are entered into a preliminary mixed model analysis. A second mixed model analysis will be conducted with intercept, PCA, and all covariates that reach $p < 0.10$ in the preliminary analysis. The covariates remaining after this screening procedure will be used in a final mixed model analysis, which will include only those variables with $p < 0.05$. This procedure will provide a parsimonious model with only centered PCA, intervention groups, and significant covariates remaining as explanatory variables. A second set of analyses will evaluate whether sleep-wake state development differs between groups following discharge. Any variables on which intervention groups differ after discharge will be included in the analysis as covariates. The same reduction procedure will be utilized.

Hypothesis # 2. Infants receiving early cycled light (28 weeks PCA) will gain weight significantly faster before and after hospital discharge than infants receiving late cycled light (36 weeks PCA), after covarying the effect of birth weight. A mixed general linear model will be used to determine whether gains in weight exhibit developmental changes over time for each intervention group. The mixed model will also be used to evaluate differences in the amounts and changes in weight gain for the two intervention groups (Andrade & Helms, 1986a, 1986b; Fairclough & Helms, 1986; Jennrich & Schluchter, 1986; Vollmer et al., 1988).

Weight will be regressed over post-conceptional age (PCA), as both a linear and quadratic trend, and intervention group. Interactions between PCA trends and intervention group will also be included in the model. Birth weight will be used as a covariate in the fixed effects component of the model because it adjusts for initial size (Morris et al., 1999). The intercept, PCA, and intervention group will be included in the random effects component to allow each infant to have his or her individual developmental trajectory. Prior to analysis, PCA will be "centered" at 28 weeks gestation, such that the 28-week data point will be scored as 0 and the other ages will be scored in weeks before or after 28 weeks.

A model reduction procedure will be employed in which each variable, including the intercept, the linear and quadratic effects of PCA, the intervention group, the PCA linear and quadratic interactions with intervention group, and birth weight, will be entered into a preliminary mixed model analysis. A second mixed model analysis will be conducted with the intercept, PCA linear and quadratic trends, intervention group, interactions between PCA and intervention group, and birth weight if significance reaches $p < 0.10$ in the preliminary analysis. Birth weight and the interaction terms remaining after this screening procedure will be used in a final mixed model analysis, which will include only those variables with $p < 0.05$. This procedure will produce a parsimonious model and simplify interpretation.

Hypothesis # 3. Infants receiving early cycled light (28 weeks PCA) will have significantly fewer hospital day, than infants receiving late cycled light (36 weeks PCA), when the effect of severity of illness and birth weight are covaried. Physiologic health and maturation, as measured by the natural logarithm of hospital days, will be assessed using analysis of covariance (ANCOVA). The natural logarithm will be used because LOS is highly skewed. This analysis will allow for comparison of group means explained by a variety of factors (Maxwell & Delaney, 1990). In the analysis, the natural logarithm of hospital days will be an outcome variable that is explained by the intervention group, birth weight, full growing calories and the interaction between intervention and birth weight and birth weight and full growing calories. The covariates have been related to LOS (Brandon et al., 2002; Lucas et al., 1996; Morris et al., 1999).

Hypothesis # 4. Infants receiving early cycled light (28 weeks PCA) will develop retinopathy of prematurity (ROP) significantly more slowly before hospital discharge than infants receiving late cycled light (36 weeks PCA), after covarying the effect of length of mechanical ventilation. To test this hypothesis, the general estimating equation (GEE) procedure (Zeger et al., 1988) will evaluate differences in ROP development. The GEE is a longitudinal regression model that provides an estimate of the probability that either group will develop ROP. The GEE can be conceptualized as ordinal logistic regression for correlated outcomes.

ROP will be coded as none, immature retina, and stages of disease. To determine if intervention groups are predictive of the development of ROP, a GEE will be calculated for ROP with the intercept, intervention group, and PCA as both a linear and quadratic trend. The interactions between the PCA trends and intervention group will also be included in the model. Birth weight and the natural logarithm of mechanical ventilation, which has been related to the development of ROP, will be included as covariates in the preliminary model (Isenberg, 1994; Urrea & Rosenbaum, 1994).

A model reduction procedure will be utilized in which each variable, including intercept, intervention group, the linear and quadratic effects of PCA, the PCA linear and quadratic interactions with intervention group, and the covariates will be entered into a preliminary GEE analysis. A second GEE analysis will be conducted with intercept, PCA linear and quadratic trends, intervention group, the interactions between PCA and intervention group, and all covariates that reach $p < 0.10$ in the preliminary analysis. The covariates and interaction terms remaining after this screening procedure will be used in a final mixed model analysis that includes only those variables with $p < 0.05$. This procedure will produce a parsimonious model and simplify interpretation.

Additional analyses will evaluate the effects of early development of ROP on the severity of ROP and visual outcomes.

Hypothesis # 5. Infants receiving early cycled light (28 weeks PCA) will have significantly better visual acuity (preferential looking test) at 12 months corrected age than infants receiving late cycled light (36 weeks), after covarying the effects of birth weight and ROP. Analysis of covariance (ANCOVA) will be used to assess group differences in visual acuity at 1 year of age. This analysis will allow for comparison of group means explained by a variety of factors (Maxwell & Delaney, 1990). Severity of ROP and birth weight will be used as covariates in the analysis because of their ability to affect visual acuity.

Hypothesis # 6. Infants receiving early cycled light (28 weeks PCA) will have significantly better neurological outcome at 9 and 18 months corrected age than infants receiving late cycled light (36 weeks PCA). A chi-square analysis will be used to evaluate group differences on the neurological exam (Hays, 1988). Items on the neurological exam will be scored as normal, suspect, or abnormal on a 0-4 scale according to functional impairment.

Hypothesis # 7. Infants receiving cycled light (28 weeks PCA) will have significantly better developmental outcomes (cognitive, motor, and language) at 9 and 18 months corrected age than infants receiving late cycled light (36 weeks PCA). Multivariate analysis of variance will be used to test for differences in mean development vectors between the intervention groups. Analysis of variance will be used to follow up statistically significant multivariate effects.

Exploratory analyses. Additional analyses will evaluate the effects of early development of ROP on the severity of ROP and visual acuity outcomes. Severity of ROP and visual acuity outcomes will be assessed using multivariate regression models. ROP and visual acuity will be modeled including the gestational age at which ROP is first diagnosed, the stage of ROP at that point, and intervention group. This analysis will allow for comparison of groups based on the gestational age and severity of ROP at initial onset.

Infants in the two different light groups are not expected to differ in the incidence of abnormal audiological findings as measured by the brainstem auditory evoked potential (BAER). Chi square procedures (Hays, 1988) will be used to assess differences between groups. Results will be categorized as

pass, fail/pass (failed in the hospital, passed repeat), or fail/fail (failed in both the hospital and repeat after discharge). Analyses will be conducted for the right ear, left ear, and for any failure, regardless of which ear.

The light intervention effects are not expected to differ as a function of gender or ethnicity. Since the outcome variables are categorical, logistic regression models will be used to compare gender-ethnicity factor combinations.

E. HUMAN SUBJECTS

I. Subject characteristics.

This study examining the effects of different points of introduction of cycled light on growth and development will include 140 prematurely born neonates. The nature of the research hypotheses requires use of preterm infants (child inclusion). Inclusion criteria are:

1). < 48 hours of age or still receiving phototherapy,
2). approval of subject's physician,
3). 23-28 weeks gestational age (by **Ballard et al., 1991**),
4). parental consent,
5). cared for in incubator or bassinet,
6). English speaking parents, and
7). no history of known anomalies associated with neurological or visual problems (e.g., congenital glaucoma, Down Syndrome).

Multiple births will be included, but each set of multiples will be randomized to the same intervention group to provide consistency for families.

Subjects will include males and females and all English speaking families regardless of ethnicity. Previous clinical research conducted in the intensive care nursery by the principal investigator resulted in approximately 68% African-American, 30% Caucasian, and 2% Hispanic/American Indian subjects. Predicted enrollment characteristics for this study are included in the Human Subjects Table, based on Duke ICN data over the past 5 years. These statistics are comparable to the statistics on neonates born prematurely in the state of North Carolina, where prematurity is highest among the African-American population.

II. Data sources.

All research data will be obtained from recordings of physiologic data (e.g., respiratory rate in the sleep-wake state recording), and pencil and paper instruments specifically for research purposes, or from existing medical record data. There are no blood, body fluid or tissue specimens involved in this research.

III. Recruitment and Consent Procedures.

Approval of the attending physician will be obtained for all infants prior to approaching parents for consent. Mothers at risk for delivering preterm are often hospitalized prior to the initiation of labor for close monitoring and bed rest. Mothers hospitalized $\leq$ 28 weeks gestation will be approached antenatally for consent if the mother is medically stable (e.g., not in active labor or requiring intensive care). Other parents will be approached for consent as soon as the mother has recovered from delivery and the parents are available for informed consent. The project coordinator, research assistant or an investigator will obtain consent for all subjects. The study will be explained, potential risks will be described, parents will be given time to ask questions, one parent will sign the consent form, and a copy of the consent form will be given to the parents. Following randomization of the infant to an intervention group, the parents will be informed of the intervention assignment and the intervention protocol for their infant.

The study investigator has had previous success in recruiting minority subjects. **Based on the preliminary study, approximately 70% of the subjects are expected to be African Americans**. To continue success in recruiting minority subjects, efforts will be made to hire at least one minority research assistant to assist with subject recruitment and retention.

IV. Potential Slubject Risks.

Data and Safety Monitoring Plan. The interventions used in this study are accepted national care practices in NICUs, including the use of incubator and bassinet covers. The covers do not place the infant at risk, because of continuous physiologic monitoring in the nursery settings. Nurse caregiving during times of near darkness can safely continue with the front flap back on the incubator covers and with the use of pen lights for close observations (e.g., peripheral intravenous catheter sites).

Every effort will be made to minimize any possible disruptions in health care that may be caused by data collection related to intervention group assignment. Sleep-wake state recording assessments during hospitalization will be coordinated with nurse caregiving and parent visitation.

It is not anticipated that participation in this study will cause harm or distress to the neonates. The EOG leads to be used for measuring rapid eye movements in the sleep-wake state recording should not cause any damage to the skin of the neonates, since they will all be at least 2 weeks old at the time of the first recording. All clinical research conducted in the Duke University Medical Center Intensive Care Nursery is approved by the medical director and chief of neonatology, Dr. Ronald Goldberg. Dr. Goldberg has written a letter of support for the proposed research.

Two potential risks exist, one with each of the study intervention groups. In the preliminary study, infants receiving cycled light at 32 weeks PCA had more auditory failures than the infants receiving cycled light at 36 weeks PCA. Even though this intervention is not one of those proposed for this study, auditory failures will be monitored to ensure intervention safety. In addition, infants receiving cycled light at 36 weeks PCA in the preliminary study experienced development of ROP earlier in gestation than infants exposed to cycled light at birth. Though it is unclear whether earlier ROP results in poorer visual outcomes, this is another potential risk that will be monitored. The only other anticipated risk is the small risk of violating the confidentiality of a subject, since names and addresses of subjects must be maintained throughout the 24-month follow-up period.

To ensure the safety of participants, a data safety and monitoring board has been established for this study; board members will include Dr. Michael Cotten, neonatologist and Duke IRB member, Richard Landerman, statistician, Diane Holditch-Davis, Professor, UNC School of Nursing and grant consultant, and Laura Enyedi, Duke pediatric opthalmologist. As the study statistician, Dr. Landerman will provide preliminary statistical analyses for the DSMB to review every 6 months. The board will meet in closed session and will have the authority to seek additional safety measures. In addition, the DSMB will be informed of any adverse events. The DSMB monitoring plan will be approved by the IRB.

Role of the investigative team. Dr. Brandon, principal investigator, will have primary responsibility for conducting the study and monitoring the research assistants. All assistants will receive training on subject recruitment, obtaining informed consent, and protecting human subjects. Dr. Brandon will also have primary responsibility for monitoring the data collection procedures and data collectors. All data collectors and recruitment nurses will be trained in study protocols by Dr. Brandon, other investigators, and the study consultants. Dr. Brandon or the project director will meet with the research nurses either in person or by phone at least every other week to ensure that they are following study protocols and not encountering any problems. Dr. Brandon and/or the project director will meet with the data collectors, either individually or in a group, at least every month to study progress, provide consultation, ascertain that data collectors are following protocols, and identify any potential adverse reactions. In addition, the project manager will check all data for completeness weekly following subject enrollment.

Dr. Landerman, study statistician, will be in charge of data analysis. He will oversee development of data entry screens, supervise data entry verification, and work with the other investigators in conducting all data analyses.

The investigators, Drs. Brandon, Goldstein, Freedman, Landerman, and Gustafason (either in

person or by phone), will meet every other week to monitor the study's progress and compare the progress of the intervention protocol, data collection, and data management. Any adverse events noted by anyone will be immediately reported to the principal investigator. In consultation with the study team, she and the infant's physician will determine if the event is study related. Study related adverse events will be reported to the IRB and NIH. The focus of investigator meetings will be on developing strategies to prevent adverse events and to monitor the research staff and ensure data integrity.

Role of the monitoring board. The DSMB, including Dr. Michael Cotten, neonatologist and Duke IRB member, Richard Landerman, statistician, Diane Holditch-Davis, Professor, UNC School of Nursing and grant consultant, and Laura Enyedi, Duke pediatric opthalmologist, will review the data monitoring and safety procedures at least bi-annually. These reviews will be conducted 6 months after the initiation of subject enrollment and every 6 months thereafter. Dr. Michael Cotton will chair the monitoring board. In addition, should any serious adverse event occur, the monitoring board will be informed immediately, and a special session will be scheduled to discuss strategies to deal with the problem.

The monitoring board meeting will included a synopsis of protocol and design, discussion of the status of the intervention and data collection procedures, a summary of subject contacts, discussion of any adverse reactions or any potential adverse reactions, the status of data entry and verification, and a summary of any descriptive and inferential statistics to date. In addition, interim analyses comparing the two interventions will be conducted with special attention given to the auditory and visual outcome variables. The monitoring board will be given time to meet in closed session without the investigators to discuss the need for additional procedures to prevent adverse reactions or ensure data integrity and the unlikely case that the study may need an early termination due to unexpected adverse reactions or inadequate administration of the conduct of the study. Recommendations from the monitoring board meetings will be shared with the IRB and NIH during annual reports and immediately if the monitoring board identifies study related adverse events not previously reported or recommends early termination of the study.

Role of the IRB. This study will recruit subjects from Duke University Medical Center in Durham, NC. The intervention will be conducted at both Duke University Medical Center and Durham Regional Hospital. The Duke University Health System IRB oversees protection of human subjects at both institutions. IRB approval of the study protocol and data safety-monitoring plan is pending. Annual progress reports and renewals will be provided, including a summary of the recommendations of the monitoring board. If any adverse events judged to be study related are noted, Dr. Brandon will immediately report them to the IRB.

Role of NIH. Summaries of the protocol and design, status of the intervention and data collection procedures, summary of subject contacts, discussion of any adverse reactions or any potential adverse reactions, status of data entry and verification, a summary of any descriptive and inferential statistics to date, and the recommendations of the monitoring board will be included in each annual report to NIH. In addition, should any adverse reaction occur or should the monitoring board recommend early termination of the study, the information will be immediately reported to the program officer at NIH.

V. Confidentiality.

To ensure confidentiality, subject numbers will identify subjects' files. All data will be stored in locked files under the direct supervision of the principal investigator.

VI. Risk vs. Benefits.

Each infant may or may not benefit from intervention group assignment since it is unclear which intervention protocol is most beneficial for preterm infants. However, since both lighting conditions are used in nurseries throughout the United States, there is only minimal risk to subjects.

MINORITIY INCLUSION

The study investigator has had previous success in recruiting minority subjects. **Based on the preliminary study, at least 60% of the subjects are expected to be African Americans**. To continue success in recruiting minority subjects, efforts will be made to hire at least one minority research assistant to assist with subject recruitment and retention. An African American women's health researcher will monitor and make recommendations for recruitment strategies throughout the study.

INCLUSION OF CHILDREN

This study will utilize children (preterm infants born $\leq$ 28 weeks gestation), both males (55%) and females (45%), and a significant number of African Americans (62%). Because the research hypotheses are exclusive to preterm infants, other children will be excluded from study participation.

From: Higgins, Rosemary (NIH/NICHD)
To: Wally Carlo, M.D.; nfiner@ucsd.edu; Edward Donovan; sduara@miami.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu
Cc: Petrie, Carolyn
Subject: RE: Pulse ox pilot
Date: Monday, April 25, 2005 12:02:00 PM

Wally

Carolyn will be setting up a SUPPORT Call and this can be discussed.

Thanks

Rose

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, April 25, 2005 11:49 AM
To: nfiner@ucsd.edu; Edward Donovan; Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu
Subject: RE: Pulse ox pilot

Dear SUPPORT subcommittee:

I am concerned that we may not be collecting the data for the pilot in enough babies and that we need to be evaluating compliance with the O2 intervention.

Currently only three centers may be in the pilot. We need to get to two hundred babies as we planned. So it would be great if we could do the pilot in all 5 core centers.

I also want to start looking at the first downloads on babies from all centers to assess compliance.

Maybe we need a conf call to agree on a plan of action.

wally

From: Higgins, Rosemary (NIH/NICHD)
To: Petrie, Carolyn
Subject: FW: SUPPORT Enrollment
Date: Thursday, April 21, 2005 9:41:00 AM

For SUPPORT

-----Original Message-----
From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Thursday, April 21, 2005 9:35 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT Enrollment

Rose,
Here are the enrollment numbers (from the data forms that have been keyed and transmitted). It's obvious that the Eligiblity form has not been keyed from all of the sites. I guess we need to remind them to key these ASAP so we can keep up with the enrollment. I know that Indiana and Alabama have also enrolled but we don't have their data.

Center 11 (Cincinnati) 2
Center 14 (Brown) 7
Center 18 (Houston) 4
Center 22 (UCSD) 2 (I know they have more than this)

Betty

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org <mailto:bkh@rti.org>

From: Wade Rich
To: "HOLLY L MINCEY"
Cc: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: RE: SUPPORT Oximetry
Date: Wednesday, April 20, 2005 3:23:33 PM

Holly,

The system the Network is putting in place will include having 10 extra oximeters placed strategically at each of 5 sites throughout the network. (Your closeset site will be Case.) This has not happened yet. Until such time, borrowing from a friendly neighbor is the best choice. I would try and borrow one sooner rather than later, but you know your system better than I do.
Wade

-----Original Message-----
From: HOLLY L MINCEY [mailto:minceyhl@uc.edu]
Sent: Wednesday, April 20, 2005 11:55 AM
To: wrich@ucsd.edu; Vivek.Narendran
Subject: SUPPORT Oximetry

Wade and Vivek,

We have an interesting "potential" situation at Good Samaritan Hospital. I would appreciate your input.
We have one patient enrolled and delivered, assigned to an orange oximeter (still in use although almost 72hours room air).
As of today, we have now consented two singleton Mom's and one Triplet gestation Mom. Thus, we may "potentially" have FIVE births. With this said we have three orange oximeters available and four blue oximeters available. If the triplet assignment should be orange, and one singleton assignment to orange, we would not have the available equipment. I realize this may be extending the possibility but at the same time I feel it is important to be prepared and have a well thought out plan in place if such an occasion should happen.
The window of opportunity exists between now, 04-20-05 and 05-04-05 at midnight.
The first thought I had was to borrow an oximeter with the appropriate assignment from University Hospital (this would require an expedited Clinical Engineering response), but I want to ensure this is correct. Also the thought to Fed Ex an oximeter at the time of need (time constraints considered).

Keep me posted,

Thanks,
Holly Mincey, BSN

From: Laroia, Nirupama
To: "Morris, Brenda H"; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; Krisa VanMeurs (VanMeurs, Krisa); cotte010@mc.duke.edu; susie.buchter@oz.ped.emory.edu; Vivek.Narendran@cchmc.org; vineet.bhandari@yale.edu; Angelita Hensman; Becky bara; Bethany Ball; Cathy Grisby; Ellen Hale; Mcdavid, Georgia E; Kathy Auten; Reubens, Linda; Lucy Miller; Monica Collins; Nancy Miller; Nancy Newman; Nancy Peters; pat.gettner@yale.edu; Ruth Everett; Wade RIch; alaptook@wihri.org; Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Phelps, Dale; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O"Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E; Walid Salhab (Walid Salhab)
Subject: RE: SUPPORT recruiting tool
Date: Monday, April 18, 2005 4:05:38 PM

After a lot of deliberation, we at Rochester have decided not to use the bracelets at this time.

We developed a running list of mom's that were approached, date consented, and when they would reach exclusion criteria (for the COIN study). This way we are able follow them even when they are discharged and readmitted. The list stays in the NICU. The fellows and the DR nurses from the NICU are aware of the names on the list. The bracelets will not help us if she reached 28 weeks with out having to calculate it in some way.

Nirupama Laroia

-----Original Message-----
From: Morris, Brenda H [mailto:Brenda.H.Morris@uth.tmc.edu]
Sent: Thursday, April 14, 2005 4:01 PM
To: Higgins, Rosemary (NIH/NICHD); kurt.schibler@cchmc.org; Krisa VanMeurs (VanMeurs, Krisa); cotte010@mc.duke.edu; Laroia, Nirupama; susie.buchter@oz.ped.emory.edu; Vivek.Narendran@cchmc.org; vineet.bhandari@yale.edu; Angelita Hensman; Becky bara; Bethany Ball; Cathy Grisby; Ellen Hale; Mcdavid, Georgia E; Kathy Auten; Reubens, Linda; Lucy Miller; Monica Collins; Nancy Miller; Nancy Newman; Nancy Peters; pat.gettner@yale.edu; Ruth Everett; Wade RIch; alaptook@wihri.org; Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Phelps, Dale; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E; Walid Salhab (Walid Salhab)
Subject: RE: SUPPORT recruiting tool

Can we get an idea about what the price would be? We would need about 2,000-3,000 if we allow for moms who do not deliver in the window. Brenda Morris

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, April 14, 2005 12:36 PM
To: Kurt Schibler (Kurt Schibler [kurt.schibler@cchmc.org]); Krisa VanMeurs (VanMeurs, Krisa); Morris, Brenda H; Michael Cotten (cotte010@mc.duke.edu); Laroia, Nirupama; susie.buchter@oz.ped.emory.edu; Vivek.Narendran@cchmc.org; vineet.bhandari@yale.edu; Angelita Hensman; Becky bara; Bethany Ball; Cathy Grisby; Ellen Hale; Mcdavid, Georgia E; Kathy Auten; Linda Reubens; Lucy

Miller; Monica Collins; Nancy Miller; Nancy Newman; Nancy Peters; Pat Gettner (pat.gettner@yale.edu); Ruth Everett; Wade RIch; Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E; Walid Salhab (Walid Salhab)
Subject: FW: SUPPORT recruiting tool

HI, Please let Michele know if you are interested in getting bracelets for your SUPPORT subjects.

Thanks
Rose
-----Original Message-----
From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Thursday, April 14, 2005 11:28 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT recruiting tool

Rose:
We are investigating getting bracelets like the Lance Armstrong one's made for women enrolled in SUPPORT to wear. We plan on alternating pink and blue with the word "SUPPORT" stamped on it. We think this might be an added trigger for identification by personnel when the women are readmitted or moved back and forth to L&D. We have a supplier identified. The cost is cheaper with the more that are made. Could you forward this to other coordinators and PIs and see if they would be interested. Current cost is 50 cents-89 cents/ each depending on volume. Regards, Michele

From: Thomson, Merran
To: Neil Finer; higginsr@mail.nih.gov.
Subject: FW: DSMC Monitoring--SUPPORT Trial
Date: Monday, April 18, 2005 1:26:47 PM
Attachments: DSMC Monitoring Memo 4-4-05 2.doc
3.2. 05 DSMC Monitoring adrev1.doc

Sorry for the delay in replying; I was (b) (6)

I would support the use of the attached figures and stats
Best wishes
Merran

Merran Thomson
Consultant Neonatologist
Chief of Service
Division of Paediatrics
5th Floor Hammersmith House
Hammersmith Hospital
Du Cane Road
London W12 0HS
PA Marianna Loizia Tel 020 8383 3270
Tel 020 8383 2471 (direct line) Fax 020 8740 8281
Switch 020 (b) (6) (b) (6) Bleep (b) (6)

-----Original Message-----
From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: 04 April 2005 17:58
To: ckr3+@pitt.edu; cgleason@u.washington.edu; (b) (6); md511@columbia.edu; rjb6j@hscmail.mcc.virginia.edu; huntc@nhlbi.nih.gov; mcallen@jhmi.edu; Thomson, Merran
Cc: higginsr@mail.nih.gov; [SCRN] Willinger, Marian; Berberim@nhlbi.nih.gov; Jobea0@chmcc.org; edward.donovan@chmcc.org; nfiner@ucsd.edu; sduara@miami.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; Das, Abhik; Poole, W. Kenneth; Gantz, Marie
Subject: DSMC Monitoring--SUPPORT Trial

Attached are the following two documents relating to the Support Trial:

- A memo to the SUPPORT Data and Safety Monitoring Committee
- A document containing suggested guidelines to aid the DSMC in monitoring the SUPPORT Trial.

Please let us know if you have any comment or questions about this material.

<<DSMC Monitoring Memo 4-4-05 2.doc>> <<3.2. 05 DSMC Monitoring adrev1.doc>>

Thanks
Betty

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

RTI INTERNATIONAL

Memorandum

April 4, 2005

TO: SUPPORT Trial Data Safety and Monitoring Committee

FROM: The Data Coordinating Center
Dr. Rosemary Higgins, NICHD
Support Trial Subcommittee

SUBJECT: Data and Safety and Monitoring Plans for the SUPPORT Trial

Attached is a document containing suggested guidelines to aid the DSMC in monitoring the SUPPORT Trial. This document, prepared by the SUPPORT Trial Subcommittee, contains rates and ranges of various common neonatal complications seen in this population of infants at neonatal research network sites. This information is provided to the DSMC as a guide for relative rates of complications in the population currently being enrolled for the SUPPORT Trial.

Please send any comment/concerns you may have to Dr. Neil Finer (Chair, SUPPORT Subcommittee) nfiner@ucsd.edu or Dr. Rosemary Higgins (Program Scientist, NICHD) higginsr@mail.nih.gov.

April 4, 2005

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial

DATA AND SAFETY MONITORING PLANS

Adverse Events

Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

As background information to help the DSMC monitor this trial, we are providing the following observational data from the network's generic database from January 1, 2002 - December 31, 2004. The proportions listed give the overall rate of an adverse event in the network population for each of the gestational age subgroups. The range of proportions for each adverse event across centers is presented to provide an idea about the variation seen over the sites for these outcomes. It is hoped that this information will provide detailed background statistics regarding the population for study in this trial.

It is suggested by the SUPPORT Subcommittee that consideration for a recommendation to stop the trial based on a safety concern would need to involve a statistically significant difference in an adverse event between the treatment groups, and that the occurrence of the adverse event is outside of the limits of plausibility for that specific event according to the most recent Neonatal Research Network data presented below.

Table 1: Overall proportion, variability and ranges across network centers for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	3753	0.237	0.43	0.108-0.371
DR Chest compressions	4050	0.108	0. 31	0.035-0.258
Pneumothorax	3861	0.087	0..29	0.023-0.195
Death within first 14 days	4055	0.159	0.37	0.092-0.325

Table 2: Overall proportion, variability and ranges across network centers for infants with gestational age 24-25 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	1599	0.327	0.47	0.153-0.520
DR Chest compressions	1805	0.133	0. 34	0.029-0.340
Pneumothorax	1667	0.116	0. 32	0.026-0.239
Death within first 14 days	1808	0.249	0.44	0.124-0.485

Table 3: Overall proportion, variability and ranges across network centers for infants with gestational age 26-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	2154	0.170	0.38	0.022-0.263
DR Chest compressions	2245	0.088	0.29	0.034-0.200
Pneumothorax	2194	0.066	0.25	0.022-0.155
Death within first 14 days	2247	0.086	0.28	0.039-0.160

Note: The sample includes infants that were born on or after January 1, 2002 that have reached status. SD denotes standard deviation.

Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. O'Brien-Fleming[i] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

From: William Oh
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Angelita Hensman; Abbot Laptook
Subject: RE: oximeters
Date: Thursday, April 14, 2005 7:43:39 PM

You are welcome and I will cc this to Angelita as a kudo

Bill

William Oh, MD
Professor of Pediatrics
Brown Medical School
Attending Neonatologist
Women and Infants Hospital
101 Dudley St,
Providence RI 02905
office phone 401 274-1122 ext 1432
cell 401 714(b)

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thu 4/14/2005 7:14 PM
To: William Oh
Subject: Re: oximeters

Bill
Angelita had sent me this. We also had Yale ship you two oximeters in the event that the consented moms deliver. An immense thanks to Angelita for the heads up. We will put into place a mechanism to obtain additional oximeters from several sites during the course of the study.
Again, thanks for all the effort!
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: William Oh <WOh@WIHRI.org>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Thu Apr 14 16:47:34 2005
Subject: FW: oximeters

Rose: FYI

Bill

William Oh, MD
Professor of Pediatrics
Brown Medical School
Attending Neonatologist
Women and Infants Hospital

101 Dudley St,
Providence RI 02905
office phone 401 274-1122 ext 1432
cell 401 714(b)

From: Pamela Celona
Sent: Thu 4/14/2005 2:20 PM
To: Angelita Hensman
Cc: Abbot Laptook; William Oh; Petrina Babcock
Subject: RE: oximeters

Angelita,

You can go ahead with the pre-award purchase. I will just make sure that the 20K comes out of the new award budget when we receive it. I'm sure the NIH is going to give us the new award, so I am confident that there will not be a problem.

Pamela Celona
Grant Manager, Fiscal Services
Women & Infants' Hospital
101 Dudley Street
Providence, RI 02905
P: (401)274-1122 ext 2156
PCelona@wihri.org

From: Angelita Hensman
Sent: Wednesday, April 13, 2005 4:59 PM
To: Pamela Celona
Cc: Abbot Laptook; William Oh; Petrina Babcock
Subject: FW: oximeters
Importance: High

Hi Pam,
We need to purchase about 10 more pulse oximeters for the SUPPORT study. The cost per unit is $2,000. Total cost $20,000. We anticipate getting these funds on the next award .However, I have been told the award is not going to be out for a while and we urgently need the pulse oximeters to keep up with the rate of enrollment at our site. I have spoken to Dr. Higgins at the NICHD and she has asked if our grants office (Fiscal) can approve the purchase as a pre-award advance (see below). If this is not possible we need to send in a letter to get approval to use our unobligated (carry over) funds. The letter will need to be signed by Dr. Oh and Fiscal. Please let me know how we should proceed on this ASAP.
Thanks
Angelita

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, April 13, 2005 4:38 PM
To: Angelita Hensman; William Oh
Cc: Poe, Grace (NIH/NICHD)
Subject: oximeters

Angelita and Bill -

In order to purchase additional oximeters in advance of the anticipated capitation award for the SUPPORT study for this year, can your grants office approved a pre-award advance for you to purchase 10 additional oximeters? If not, a request to use previously awarded or carryover funds signed by Dr. Oh and the grants office is needed and you may fax it to us.

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Maynard Rasmussen, MD
To: Michele Walsh
Cc: Higgins, Rosemary (NIH/NICHD) [E]; wrich@ucsd.edu
Subject: RE: SUPPORT recruiting tool
Date: Thursday, April 14, 2005 5:21:54 PM

Michele,
Excellent idea. I would like to order ~75 of them for Sharp. Depending on how this works, we may want to use color coded bracelets for our other studies also (i.e. Candida)
Thank-you
Maynard

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, April 14, 2005 11:15 AM
To: Maynard Rasmussen, MD
Subject: FW: SUPPORT recruiting tool

Maynard
Let Michele know if you are interested.
Thanks
Rose
-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD)
Sent: Thursday, April 14, 2005 1:36 PM
To: Kurt Schibler (Kurt Schibler [kurt.schibler@cchmc.org]); Krisa VanMeurs
(VanMeurs, Krisa); Brenda Morris (Brenda.H.Morris@uth.tmc.edu); Michael Cotten (cotte010@mc.duke.edu); 'Laroia, Nirupama'; 'susie.buchter@oz.ped.emory.edu'; 'Vivek.Narendran@cchmc.org'; 'vineet.bhandari@yale.edu'; Angelita Hensman; Becky bara; Bethany Ball; Cathy Grisby; Ellen Hale; Georgia McDavid; Kathy Auten; Linda Reubens; Lucy
Miller; Monica Collins; Nancy Miller; Nancy Newman; Nancy Peters; Pat Gettner (pat.gettner@yale.edu); Ruth Everett; Wade RIch; Abbot Laptook (alaptook@WIHRI.org); 'Abhik Das'; 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; 'Charles Rosenfeld'; 'Dale Phelps'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; 'Jobe Alan (E-mail)'; 'Lemons Jim (E-mail)'; 'Michael O'Shea'; 'Michelle Walsh'; 'Neil Finer'; 'Oh William (E-mail)'; 'Poole Kenneth (E-mail)'; 'Ronald GOldberg'; 'Shahnaz Duara'; 'Shankaran Seetha (E-mail)'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon
(E-mail)'; Walid Salhab (Walid Salhab)
Subject: FW: SUPPORT recruiting tool

HI, Please let Michele know if you are interested in getting bracelets for
your SUPPORT subjects.

Thanks
Rose
-----Original Message-----

From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Thursday, April 14, 2005 11:28 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT recruiting tool

Rose:
We are investigating getting bracelets like the Lance Armstrong one's made
for women enrolled in SUPPORT to wear. We plan on alternating pink and blue
with the word "SUPPORT" stamped on it. We think this might be an added
trigger for identification by personnel when the women are readmitted or
moved back and forth to L&D. We have a supplier identified. The cost is
cheaper with the more that are made. Could you forward this to other
coordinators and PIs and see if they would be interested. Current cost is
50 cents-89 cents/ each depending on volume. Regards, Michele

From: Angelita Hensman
To: Pamela Celona
Cc: Abbot Laptook; William Oh; Petrina Babcock
Subject: RE: oximeters
Date: Thursday, April 14, 2005 2:50:13 PM

Thanks Pam. I will put the order in today and will send it to you to authorize and forward to purchasing.
Angelita

From: Pamela Celona
Sent: Thursday, April 14, 2005 2:21 PM
To: Angelita Hensman
Cc: Abbot Laptook; William Oh; Petrina Babcock
Subject: RE: oximeters

Angelita,

You can go ahead with the pre-award purchase. I will just make sure that the 20K comes out of the new award budget when we receive it. I'm sure the NIH is going to give us the new award, so I am confident that there will not be a problem.

Pamela Celona
Grant Manager, Fiscal Services
Women & Infants' Hospital
101 Dudley Street
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From: Angelita Hensman
Sent: Wednesday, April 13, 2005 4:59 PM
To: Pamela Celona
Cc: Abbot Laptook; William Oh; Petrina Babcock
Subject: FW: oximeters
Importance: High

Hi Pam,
We need to purchase about 10 more pulse oximeters for the SUPPORT study. The cost per unit is $2,000. Total cost $20,000. We anticipate getting these funds on the next award .However, I have been told the award is not going to be out for a while and we urgently need the pulse oximeters to keep up with the rate of enrollment at our site. I have spoken to Dr. Higgins at the NICHD and she has asked if our grants office (Fiscal) can approve the purchase as a pre-award advance (see below). If this is not possible we need to send in a letter to get approval to use our unobligated (carry over) funds. The letter will need to be signed by Dr. Oh and Fiscal. Please let me know how we should proceed on this ASAP.
Thanks
Angelita

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, April 13, 2005 4:38 PM
To: Angelita Hensman; William Oh
Cc: Poe, Grace (NIH/NICHD)
Subject: oximeters

Angelita and Bill -
In order to purchase additional oximeters in advance of the anticipated capitation award for the SUPPORT study for this year, can your grants office approved a pre-award advance for you to purchase 10 additional oximeters? If not, a request to use previously awarded or carryover funds signed by Dr. Oh and the grants office is needed and you may fax it to us.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT screening and eligibility form
Date: Wednesday, April 13, 2005 1:19:47 PM

perhaps she could use Neopuff funds...

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, April 13, 2005 10:12 AM
To: wrich@ucsd.edu
Subject: RE: SUPPORT screening and eligibility form

I will get a time frame this afternoon. I spoke to Angelita and we will attempt to address the acute issue of possibly not enough oximeters later today.
Thanks
Rose

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, April 13, 2005 1:02 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT screening and eligibility form

when is the money planned to arrive/?
w

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, April 13, 2005 9:38 AM
To: wrich@ucsd.edu
Subject: RE: SUPPORT screening and eligibility form

We are going to do this. If she is worried, I can work with the grants office to move this forward so they can get them, but grants management needs to approve.
Thanks
Rose

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, April 13, 2005 12:36 PM
To: Higgins, Rosemary (NIH/NICHD)
Cc: nfiner@ucsd.edu
Subject: FW: SUPPORT screening and eligibility form

Rose,
My take of what you said is that the "extra" units are not funded yet, correct? So, do I advise Angelita to not cosent what she can not guarantee enrollment for?
Wade

From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Wednesday, April 13, 2005 9:16 AM
To: wrich@ucsd.edu
Cc: bkh@rti.org
Subject: SUPPORT screening and eligibility form

Hi Wade,
Let me know if there's anything I can do to help with the above forms.

Betty : What is the process if say at the end of the week I need another pulse oximeter?

P.S . We have 6 enrolled to date. 3 are on orange p.o and we have about 4 consented, one with twins.
None of them may deliver but then again.....
Thanks
Angelita

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT screening and eligibility form
Date: Wednesday, April 13, 2005 12:44:13 PM

Sorry.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, April 13, 2005 12:43 PM
To: Hastings, Betty J.
Subject: RE: SUPPORT screening and eligibility form

This is the second email – I will call Angelita
Thanks
Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Wednesday, April 13, 2005 12:42 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: FW: SUPPORT screening and eligibility form

Rose,
We don't have anything set up to deal with this situation yet do we?

-----Original Message-----
From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Wednesday, April 13, 2005 12:16 PM
To: wrich@ucsd.edu
Cc: Hastings, Betty J.
Subject: SUPPORT screening and eligibility form

Betty : What is the process if say at the end of the week I need another pulse oximeter?

P.S . We have 6 enrolled to date. 3 are on orange p.o and we have about 4 consented, one with twins. None of them may deliver but then again.....
Thanks
Angelita

From: Higgins, Rosemary (NIH/NICHD)
To: Edward Donovan; Duara, Shahnaz; wcarlo@peds.uab.edu; "Neil Finer"; Michele Walsh
Cc: Das, Abhik; "Ken Poole"; Carolyn Petrie; "Betty Hastings"
Subject: FW:
Date: Friday, April 08, 2005 3:08:00 PM
Attachments: Growth Oxygenation SUPPORT secondary2.doc

Hi
Shahnaz has asked that this be circulated to the SUPPORT subcommittee in advance of the meeting. We will have a few copies available.
Have a safe trip to Washington.
Thanks
Rose

-----Original Message-----
From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Friday, April 08, 2005 1:02 PM
To: nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD); wcarlo@peds.uab.edu
Subject:

Hi Neil,

Here is the growth secondary, with your suggestions incorporated. I hope you will be able to circulate it so we can discuss it at SC.

Wally and Rose, Cristina is a young faculty member here who is interested in looking at growth in the SUPPORT babies. We tried to restrict the amount of extra labor and held off any blood work in the interest of everyone's sanity.

See you in DC
Shahnaz

Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study: A Proposed Secondary Study

Cristina Navarrete MD, Shahnaz Duara MD, Wally Carlo MD, and Neil Finer MD, University of Miami Miller School of Medicine, Miami, FL, University of Alabama, Birmingham and University of California San Diego, San Diego, CA

Abstract:

Post-natal growth retardation is a major problem in preterm infants. Perturbations in oxygenation are recognized to influence post-natal growth; hypoxic conditions can directly impair growth and hyperoxic conditions predispose infants to BPD which in turn has been linked to poor growth. The NICHD Neonatal Network is conducting a prospective trial of preterm infants randomized to two levels of baseline oxygen saturations. The effect of baseline saturations on pulmonary morbidity and ROP are the primary outcome measures. With respect to post-natal growth, there is a paucity of data that relates alterations in baseline oxygen saturation and/or frequent deviations above or below the baseline to growth outcomes. We propose an ancillary study to quantify short-term growth velocity in-hospital and long-term growth at 18-22 months of corrected age for infants enrolled in the SUPPORT Trial in relationship to oxygen saturation.

A. Hypothesis to be tested

Primary:

1. Infants randomized to the lower target oxygen saturation range (85-89%) will have better growth in hospital and at 18-22 months corrected age than infants randomized to the higher oxygen saturation range (91-95%).
2. Post-natal growth rate will be a function of actual median oxygen saturation independent of group of randomization (higher or lower oxygen saturation).

Secondary:

1. Post-natal growth will negatively correlate with the time spent with SpO2 <85% or <75%.

B. Specific Aims

1. To measure weight, length and head circumference at birth, corrected age 28w, 32w, 36w, and 18-22 months in all infants enrolled in the SUPPORT trial.
2. To determine whether achieved oxygen saturation, independent of randomization group, will affect growth velocity during in-hospital stay and growth over time, as measured at 18-22 months corrected age, in all infants enrolled in the SUPPORT trial.

C. Rationale

The SUPPORT Trial will randomize infants to two ranges of SpO2 in order to test the hypothesis that use of a lower SpO2 range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity and/or the need for surgical intervention. The growth pattern in extremely premature infants exposed to different target oxygen saturations for the entire duration of their oxygen exposure suggests poorer growth in infants exposed to higher oxygen saturations by unit policy (Tin 2001). Conversely, observational data of infants with established BPD show better growth with home oxygen support (Groothius 1987), and two recent RCT of different target saturations in oxygen-dependent premature infants show no difference in short or long-term growth outcomes (STOP-ROP 2000, BOOST Trial 2003). Therefore, this study provides the opportunity to obtain critically needed growth information on premature infants without established chronic lung disease who are exposed to different target oxygen saturation strategies from birth onwards.

D. Background

Improvements in antenatal care, respiratory support and nutrition have contributed to increased survival of ELBW infants. As the number of survivors increase, the long term outcome of these infants becomes more important. Lemons et al described growth failure or weight <10th percentile at 36 weeks postmenstrual age in 97% of ELBW infants surviving to discharge. Some morbidities in adulthood are linked to growth during the early post-natal period (Singhal 2004) and make adequacy of growth in this population of heightened interest.

Instead of following intra-uterine growth curves of age matched fetuses, VLBW infants exhibit wide-spread post-natal growth retardation (Cooke 2004), losing ground during the first weeks of life (Berry 1997). To resume growth post-natally, nutrition is of paramount importance; however, other factors such as severity of illness and perhaps oxygenation also play a role. Observational studies of infants with BPD showed poor post-natal growth when infants were sent home without oxygen supplementation (Markestad 1981).

Although preterm infants without lung disease attain oxygen saturations >95%, artificial attempts to keep arterial oxygenation at a "physiological" level may not be beneficial to growth, the lung or retina (Tin 2001). Animal studies have shown that newborn mammals (mice, rats, guinea pigs) develop poor growth with chronic hypoxia and that blunted body growth is directly proportional to the profundity of the exposure to chronic hypoxia (Mortola 1990). Chronic hypoxemia has also been suggested as the cause of poor growth in patients with cyanotic congenital heart

disease (Dundar 2000). When home oxygen supplementation was discontinued inappropriately by parents in a cohort of VLBW infants with BPD, there was a deceleration in the rate of weight gain, which improved when oxygen supplementation was resumed (Groothius 1987). Hudak et al in 1989 observed that ELBW infants with CLD who went home on oxygen supplementation had good catch-up growth at 19 months. Taken collectively, these data suggest that hypoxic conditions affect growth negatively and supplementing oxygen may improve growth.

The optimal level of oxygen saturation to promote post-natal growth is unknown. Most of the available human data is limited to oxygen supplementation of infants who are oxygen dependent or have BPD. Baraldi et al demonstrated that discharged infants with BPD, who were kept on supplemental oxygen to keep saturations above 94%, had progressive but poor weight gain (stayed below 3rd percentile) at 9 months corrected age follow-up. In infants with BPD whose oxygen supplementation was intentionally discontinued, the subset who exhibited episodes of desaturations below 88-91% had a significant decline in the rate of weight gain as compared to those who maintained saturations above 92% (Moyer-Mileur 1996). Conversely, when two different oxygen saturation control policies (high: 88-98% and low: 70-90%) were retrospectively reviewed in <28 week gestation infants, the infants being cared for in the high oxygen saturation policy units were more likely to weigh less than the 3rd percentile at discharge (45% vs. 17%, Tin 2001). The infants assigned to the high oxygen saturation limits were also more likely to have BPD and ROP.

Recently, the BOOST Trial demonstrated that randomizing infants born <30 weeks gestation who were still on oxygen at 32 weeks postmenstrual age either to standard saturations (91-94%) or to high saturations (95-98%) produced no significant difference in growth at 12 months corrected age. This study, while randomizing infants to two different levels of saturations (conventional and high), only enrolled infants if they were still on oxygen supplementation at 32 weeks PCA and used higher limits than planned by SUPPORT. Our proposal is novel in that growth will be longitudinally tracked up to 18-22 months PCA in immature infants randomized at birth to two oxygen saturation limits, with close monitoring of saturations maintained for the duration of their oxygen exposure, up to 36 weeks PCA.

E. Methods

Collection of Data (some are already part of the GDB *)

Anthropometric Measures – at birth*, corrected age 28w, 32w, 36w*, status* and 18-22 months*

1. weight
2. length
3. head circumference

Clinical Data –

1. 24 h intake (Parenteral, Enteral) – at corrected age 28w, 32w, 36w, status and 18-22 months
2. Date of first enteral feed*
3. Date of full enteral feeds (parenteral <20ml/kg/d)*
4. Total number of days on parenteral nutrition*
5. Date when infant regained birth weight*

Intervention Data –

1. Percent time in assigned target range and outside target range
2. Median value for oxygen saturation
3. Duration of oxygen use

Primary Outcome:

Growth failure (weight < 10^{th} percentile) at 36 weeks post-conception age and at 18-22 months corrected age

Sample Size:

Given the limited amount of additional growth data requested, and the wealth of oxygen saturation data that will be available for analysis, all infants in the SUPPORT Trial would ideally be recruited for this analysis (n=1320)

Statistical Analysis:

Based upon intent-to-treat, differences between treatment arms of continuous data will be assessed by the Student t-test or the Mann-Whitney U-test, depending upon normal or skewed data distribution. Categorical data will be compared by chi-square. Linear regression will be used to determine the relationship between measures of oxygen saturation and growth. Logistic regression models will be developed to determine whether oxygen saturation independently affects growth after correction for confounding variables that also alter growth.

F. Discussion of Anticipated Results

We anticipate a better growth outcome at 36 weeks PCA and at 18-22 months corrected age in the infants randomized to the lower target saturation range who maintained their median oxygen saturations within study range.

G. Budget

Time for the Research Nurses to review subject records, collect nutritional data at four fixed time points and to do additional anthropometric measurements at corrected ages 28w and 32w.

References:

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From: Higgins, Rosemary (NIH/NICHD)
To: Duara, Shahnaz; nfiner@ucsd.edu
Cc: wcarlo@peds.uab.edu
Subject: RE:
Date: Friday, April 08, 2005 1:07:00 PM

Would you like copies for the meeting and
Do you want it sent to the SUPPORT Subcommittee?
Thanks
Rose

-----Original Message-----
From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Friday, April 08, 2005 1:02 PM
To: nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD); wcarlo@peds.uab.edu
Subject:

Hi Neil,

Here is the growth secondary, with your suggestions incorporated. I hope you will be able to circulate it so we can discuss it at SC.

Wally and Rose, Cristina is a young faculty member here who is interested in looking at growth in the SUPPORT babies. We tried to restrict the amount of extra labor and held off any blood work in the interest of everyone's sanity.

See you in DC
Shahnaz

From:	Roy Heyne
To:	drfjcmd@aol.com; steichij@email.uc.edu; adusick@iupui.edu; Higgins, Rosemary (NIH/NICHD) [E]; golds005@mc.duke.edu; vjohnson@med.wayne.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; MPeralta@PEDS.UAB.EDU; petrie@rti.org; srhintz@stanford.edu; yvaucher@ucsd.edu; gary_myers@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; rdillard@wfubmc.edu; bvohr@wihri.org; richard.ehrenkranz@yale.edu
Cc:	adas@rti.org; bkh@rti.org; joa@rti.org; mcclure@rti.org; poo@rti.org; schaefer@rti.org; mbball@stanford.edu; BRUNNEMJ@UCMAIL.UC.EDU; Alice.J.Reardon@uth.tmc.edu; jrose@wihri.org
Subject:	Re: Updated FU Forms, NF12, NF05, NF05A
Date:	Thursday, April 07, 2005 4:08:32 PM

NF05: 1.d. Vision: Do we need to add "based on history +/-observation," since the manual suggests this is principally based on history, but we agreed that we should also take observation into account?

2.a Hearing: If 2.a.1 is "Yes," looks like, as it stands, we would need to answer Y or N (with detail if Y) for each of the possible hearing test types specified by items 2-4, or is there a simpler way to get at this? As to the results, does "equivocal" cover situations where the testing was partial/limited and, for that or other reasons, inconclusive?

4.b.Palpated tone: would drop "within normal range?" since these are not Y or N questions, but rather refer to the legend choices above. For #2, I would further qualify "Lower extremity muscle" with "(except for ankles)"; and I would change #3 from "Knees" to "Ankles," since that is the one angle that have further/separate ramifications for classification.

7. Primitive Relfexes: Would add "PS" for positive support, to correspond to manual.

NF05A: In the second horizontal row/tier, in the box with "Creeps.....held", the inserted word "and" should precede "cruises" rather than follow it, and should not replace "or". Might even be clearer to list each of the three items in this box on separate lines, with "and" in between the 1st and 2nd and between 2nd and 3rd lines. For the multi-item box in the 3rd row, would use the same scheme, though the 3rd item is optional, as indicated by "may." Same for the 3 items in the next row.

NF12 is o.k.

>>> "Petrie, Carolyn" <petrie@rti.org> 4/7/2005 9:39:31 AM >>>
Thanks you for participating in the form revision call earlier this week. We are making great progress! Please find updated drafts of the
NF05, NF05A and NF12. Changes are highlighted in the documents.

Provide your comments and specific information on any changes you can identify. We would like specific recommendations for the "Deep Tendon Reflexes" questions 10-13 on the NF05. (Don't worry about formatting at
this point).

I will send the announcement on our next conference call soon.

Carolyn Petrie

Neonatal Research Network Coordinator

RTI International

6110 Executive Blvd

Suite 902

Rockville, MD 20852

ph. (301) 230-4648

fx. (301) 230-4646

From:	Roy Heyne
To:	drfjcmd@aol.com; steichji@email.uc.edu; adusick@iupui.edu; Higgins, Rosemary (NIH/NICHD) [E]; golds005@mc.duke.edu; vjohnson@med.wayne.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; MPeralta@PEDS.UAB.EDU; petrie@rti.org; srhintz@stanford.edu; yvaucher@ucsd.edu; gary_myers@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; Laura.L.Whiteley@uth.tmc.edu; rdillard@wfubmc.edu; bvohr@wihri.org; richard.ehrenkranz@yale.edu
Cc:	adas@rti.org; bkh@rti.org; joa@rti.org; mcclure@rti.org; poo@rti.org; schaefer@rti.org; BRUNNEMJ@UCMAIL.UC.EDU; Alice.J.Reardon@uth.tmc.edu; jrose@wihri.org
Subject:	RE: FU conf call--revising NF05, 07 and 12 -- Mon Apr 4, 3:30pm ET
Date:	Friday, April 01, 2005 7:04:28 PM
Attachments:	NRN_NF05_comments.doc

In reviewing the changes that have been made so far to NF05 (in the March 3 draft attached below), I have the following questions/comments:

B.1.d Vision Still not clear how much this is based on history vs. exam: the form suggests exam, but the manual refers to hx. As I commented on 2/28, if we are going to use this item for the NDI of blind, then it seems we should at least specify more clearly the basis for that outcome.

B.2 Hearing I think the inserted instruction "If YES....." should be indented inside a. and numbered 2). Accordingly, the various types of audio assessment under it should be further indented and lettered a to d (instead of 1-4), with right vs. left being numbered i or ii.

B.3.b typo: dysphagia
B.3.d-e do we need to add "thickened liquids" for those children with difficulty with thin liquids?
B.3.f-h need to be indented

B.5.b Tone (actually B.4.b) Still have same questions/comments as I stated in my 2/28 e-mail attachment.

B.5 GMF Level In looking back at the algorithm and comparing to BEAM algorithm, I think what we have is still reasonable, assuming we all still agree that we should retain a "possible Level 1" which Palisano does not specifically identify. However, as I said last time, I think we should not limit this to asymmetry but should include other dysfluencies, such as toe walking and perhaps ataxias.

B.7-18 Same comments as on 2/28. In addition, note that the form only mentions 2 primitive reflexes, whereas the manual includes 3 (adding Positive Support).

I am reattaching my 2/28 comments for your reference.

>>> "Petrie, Carolyn" <petrie@rti.org> 3/31/2005 3:05:44 PM >>>
Reminder for Monday's call:

The Follow Up conference call to discuss the second half of the NF05, NF07 and NF12 is scheduled for

Monday, April 4

3:30-4:30 pm ET (12:30-1:30pm PT)

Please let me know if you are unable to join the call.

Attached is a draft revision of the NF05. Please email your comments on
these forms prior to the call.

To join the call:

Dial Tollfree: 866-675(b) (6)

Passcode: (b) (6) when prompted)

Leader: Rose Higgins

Thank you!

Carolyn

Comments/Questions on Follow-Up Forms NF05/A
Roy Heyne Dallas 2/28/05

B.1a-b. Eye: According to the manual, one is supposed to record a 1 for "consistent" tropias or for nystagmus or roving eye movements, yet the categories on the form only list esotropia or exotropia. It is also not clear how to classify "phorias;" are these "suspect".

B.1.c. Eye: According to the manual, this item appears largely based on history, but examiner observation presumably would also figure in if the latter suspected a vision problem the parents had not appreciated to the same degree. In such a case, should one be able to note the basis for the recorded finding, and/or as in item 2, specify whether the child has had or will have a formal eye exam. The BEAM exam includes an exam item related to extent of tracking, which is an indicator of vision and/or EOM control. In any case, if the answer to this item is what we are basing the blindness component of NDI on, then it would seem we need to clarify the basis for such a diagnosis/status.

B.2a Hearing: On a2, the basis/criteria for recording a Pass (vs. Fail) are not specified, nor is there provision for indicating inconclusive results. There are any number of components that could be abnormal on an audio exam, that may not conclusively indicate hearing loss; conversely, "passing" an OAE may not be sufficient to establish normal hearing, since it is really not a hearing test per se. The NF14 assists in spelling this out for the Phototherapy trial, but I'm not sure what we can make out of the info on NF05 as it stands.

B.2b Hearing: My comments on 2b are analogous to those on B1c above. It is not clear whether this determination is based solely/primarily on history, or to what extent it presumes the child has had formal hearing evaluation. Even in the latter case, it is not clear whether an OAE will suffice, or whether we need VRA; or to what extent our clinical impression of hearing should figure in. What happens if we note delayed language and suspect some possible hearing loss and refer the child for hearing evaluation? Do we defer marking this item until that is completed?

B.3 Oral Motor: How do we code situations where a child is fed through a G-tube or button to supplement an inadequate oral caloric intake, which is not due to dysphagia per se?

B.4.b Palpated Tone: The manual does not does not provide clear guidelines for differentiating between suspect and definite increased tone, nor does it specify that both moderate and marked abnormalities as defined by the listed angles are to be considered definite increased, though I presume that is the case. It is also worth noting that the angles used to indicate abnormal in the Elgan protocol are even more restricted than the "marked" cutoff here in the case of abductor and popliteal angles. In the case of decreased tone, there are no clear guidelines as to cutoffs for suspect or definite in either the manual or Amiel-Tison's book, as I read them. In the case of the upper extremities, the Elgan manual describes "resistance" to movement more in qualitative terms, rather

than in terms of angles. Another issue that pertains to either increased or decreased tone is the fact that there is no clear guideline for determining how many angles/joints need to be abnormal to call the overall extremity suspect vs. definite. Some of our inter-rater cases illustrate situations where tone is only increased in the Achilles, but normal or even somewhat decreased in heel to ear, popliteal, and/or abduction, or conversely. How should we rate such "mixed" situations. Finally, I think some comment about the need to distinguish "active resistance" (either playful or "irritable") from passive tone would be worthwhile. The Elgan protocol addresses this to some extent, but I have found this to be a tricky judgment call in some cases. Finally, on a minor format note, I like the more condensed format on the BEAM exam form, where the blanks for recording upper and lower and R and L are condensed to two juxtaposed sets of blanks.

B.5 Gross Motor Function: My comment here on the NF05A algorithm pertains to the "Symmetrical gait" criterion used to differentiate Possible Level 1 from Level 1. This criterion would appear to allow one to classify a child as Normal with a functional, symmetrical, but non-fluent gait; but I'm not sure that is the intent. The BEAM does not limit the differentiation between normal and Level 1 to symmetry.

B.6 Hand Preference: The term "consistent" may not be specific enough. The BEAM manual uses the term "exaggerated" for age and describes it better.

B.7 Primitive Reflexes: May be worth further defining "obligatory." Though the manual specifies the two minimum reflexes to check, do we check abnormal if we find persistence of other primitive reflexes, such as support (in BEAM) or Moro?

B.8 Protective Reactions: The criteria for symmetric (normal) should also include extent and timeliness of the reaction, as specified in the Elgan protocol.

B.9 Limb Movements: Would further qualify these as "spontaneous."

B.10-12 Deep Tendon Reflexes: The manual does not provide guidelines for differentiating 3+ from 4+ and we have debated this issue in prior inter-rater sessions. I would suggest adopting the differentiation between normal and abnormal spelled out in the Elgan protocol. Have we ever considered adding the adductor reflex?

B.14 Plantar Reflexes: I think it is a challenge in 18 month olds to obtain clear and consistent responses, even with deconditioning/distraction, and appropriate technique. Though I don't always repeat this 3 times as recommended in the Elgan protocol, I am satisfied if I get a clear flexor response or a repeated extensor that I don't think is a tickle or voluntary response. But I have been coding equivocal or inconsistent or hard to interpret responses as "inconsistent"

B.15c. Gait: The criteria for differentiating between normal/fluent and non-fluent are not spelled out and we have had some difference of opinions about this our inter-rater sessions.

Motor Quotient: Though the criteria for diagnosis of CP include motor delay, NF05 includes no documentation of motor quotient, whereas the BEAM form does.

B.16 Diagnoses: The threshold/criteria for diagnosing mild CP of various forms remains a challenge. The manual also provides no guidelines/examples for "Other Abnormal" vs. Other CP. It is also unclear how many "suspects" (at the extremity or even specific joint level) are needed to dx mild CP vs. other abnormal/CP. The differentiation between generalized hypotonia and hypotonic CP (+/- ataxia) is not clear. Those with truncal and appendicular hypotonia should be classified as generalized hypotonia per the manual, but what do we do with those with only truncal or only appendicular hypotonia or only partial versions of either? Finally, the manual should make clear that the presence of any suspects excludes coding the child as normal, since that is what the edits are expecting.

From: Higgins, Rosemary (NIH/NICHD)
To: Hastings, Betty J.
Cc: Poole, W. Kenneth; Das, Abhik
Subject: SUPPORT DSMC document
Date: Friday, April 01, 2005 8:55:00 AM
Attachments: 3.2. 05 DSMC Monitoring adrev.doc

Hi Betty
Can you distribute this document to the DSMC for assistance in monitoring the SUPPORT Trial? I think it is the final version.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial

DATA AND SAFETY MONITORING PLANS

Adverse Events

Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

As background information to help the DSMC monitor this trial, we are providing the following observational data from the network's generic database from January 1, 2002-December 31, 2004. The proportions listed give the overall rate of an adverse event in the network population for each of the gestational age subgroups. The range of proportions for each adverse event across centers is presented to provide an idea about the variation seen over the sites for these outcomes. It is hoped that this information will provide detailed background statistics regarding the population for study in this trial.

It is suggested by the SUPPORT Subcommittee that consideration for a recommendation to stop the trial based on a safety concern would need to involve a statistically significant difference in an adverse event between the treatment groups, and that the occurrence of the adverse event is outside of the limits of plausibility for that specific event according to the most recent Neonatal Research Network data presented below.

Table 1: Overall proportion, variability and ranges across network centers for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	3753	0.237	0.43	0.108-0.371
DR Chest compressions	4050	0.108	0. 31	0.035-0.258
Pneumothorax	3861	0.087	0..29	0.023-0.195
Death within first 14 days	4055	0.159	0.37	0.092-0.325

Table 2: Overall proportion, variability and ranges across network centers for infants with gestational age 24-25 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	1599	0.327	0.47	0.153-0.520
DR Chest compressions	1805	0.133	0. 34	0.029-0.340
Pneumothorax	1667	0.116	0. 32	0.026-0.239
Death within first 14 days	1808	0.249	0.44	0.124-0.485

Table 3: Overall proportion, variability and ranges across network centers for infants with gestational age 26-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	2154	0.170	0.38	0.022-0.263
DR Chest compressions	2245	0.088	0.29	0.034-0.200
Pneumothorax	2194	0.066	0.25	0.022-0.155
Death within first 14 days	2247	0.086	0.28	0.039-0.160

Note: The sample includes infants that were born on or after Jan 1, 2002 that have reached status. SD denotes standard deviation.

Comment [h1]:

Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. O'Brien-Fleming[i] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support oximeters
Date: Thursday, March 31, 2005 4:46:32 PM

We will be fine. I was just thinking about the other centers as we previously discussed.
wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, March 31, 2005 1:14 PM
To: 'wrich@ucsd.edu'
Cc: 'nfiner@ucsd.edu'; Poe, Grace (NIH/NICHD)
Subject: Re: Support oximeters

It is anticipated that they will be awarded in the next couple of months. If you need them sooner, neil can send a letter signed by the ucsd business official requesting to purchase them sooner.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wade Rich <wrich@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Thu Mar 31 16:07:32 2005
Subject: Support oximeters

Rose,

What is the status of the extra oximeter placements for SUPPORT ? We have already had to swap oximeters at our sites. I suspect it may become an issue. We were all assumming that every other randomization would be of a specific color. But Houston has had 4 cpap kids and Sharp has had 4 cpap kids, three of whome are orange. All of our kids have been orange also. Random means random.

Wade

Wade Rich, RRT-NPS
Clinical Research Administrator
Division of Neonatology
UCSD Medical Center
200 W Arbor Dr
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pgr 290(b) (6)

From: Higgins, Rosemary (NIH/NICHD)
To: "SDuara@med.miami.edu"
Subject: Re: SUPPORT IRB
Date: Tuesday, March 29, 2005 5:04:45 PM

This is great!!
I will hold off on the FDA thing.
Thanks!!!
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Duara, Shahnaz <SDuara@med.miami.edu>
To: nfiner@ucsd.edu <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
CC: Everett, Ruth <REverett@med.miami.edu>; Larbie, Virgie <VLarbie@um-jmh.org>; Burke, Barbara, R.N. <BBurke@um-jmh.org>; Fasone, Lucille <LFasone@um-jmh.org>
Sent: Tue Mar 29 16:51:14 2005
Subject: SUPPORT IRB

Hi Everyone,

Just called Western IRB for an update and heard good news - our IRB submission was approved at the meeting last Friday, and we will be getting something from them by the end of the week. Can't wait to start.

Shahnaz

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: wrich@ucsd.edu
Subject: RE: Enrollment
Date: Monday, March 28, 2005 9:50:02 AM

Will do
Be Well
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 28, 2005 5:38 AM
To: wrich@ucsd.edu; Neil Finer
Subject: RE: Enrollment

This is terrific - At the steering committee meeting, I think it would be good to discuss mechanistic issues that have come up so far - like compressions in the DR, pneumothoraces and adverse event reporting, etc.
Thanks
Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Tuesday, March 22, 2005 1:34 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Enrollment

10 babies in Support as of today. Rolling at last.
3 Sharp, 3 UCSD, 2 Cinn, 1 Hou., 1 Brown.
Wade

Wade Rich, RRT-NPS
Clinical Research Administrator
Division of Neonatology
UCSD Medical Center
200 W Arbor Dr
San Diego, CA 92103-8774
619-543-5375
pgr 290-(b) (6)

From: Higgins, Rosemary (NIH/NICHD)
To: Berberich, Mary Anne (NIH/NHLBI)
Subject: DSMC guidance
Date: Wednesday, March 16, 2005 12:56:00 PM
Attachments: 3 3 05 DSMC Monitoring.doc

Hi Mary Anne
Our SUPPORT Subcommittee and the Steering Committee for the Neonatal Research Network has put together a guidance document for the DSMC for the trial. Let me know if you have any suggestions prior to distribution to the DSMC members.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial

DATA AND SAFETY MONITORING PLANS

Adverse Events

Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

As background information to help the DSMC monitor this trial, we are providing the following observational data from the network's generic database from January 1, 2002-December 31, 2004. The proportions listed give the overall rate of an adverse event in the network population for each of the gestational age subgroups. The range of proportions for each adverse event across centers is presented to provide an idea about the variation seen over the sites for these outcomes. It is hoped that this information will provide detailed background statistics regarding the population for study in this trial.

It is suggested by the SUPPORT Subcommittee that consideration for a recommendation to stop the trial based on a safety concern would need to involve a statistically significant difference in an adverse event between the treatment groups, and that the occurrence of the adverse event is outside of the limits of plausibility for that specific event according to the most recent Neonatal Research Network data presented below.

Table 1: Overall proportion, variability and ranges across network centers for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	3753	0.237	0.43	0.108-0.371
DR Chest compressions	4050	0.108	0. 31	0.035-0.258
Pneumothorax	3861	0.087	0..29	0.023-0.195
Death within first 14 days	4055	0.159	0.37	0.092-0.325

Table 2: Overall proportion, variability and ranges across network centers for infants with gestational age 24-25 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	1599	0.327	0.47	0.153-0.520
DR Chest compressions	1805	0.133	0. 34	0.029-0.340
Pneumothorax	1667	0.116	0. 32	0.026-0.239
Death within first 14 days	1808	0.249	0.44	0.124-0.485

Table 3: Overall proportion, variability and ranges across network centers for infants with gestational age 26-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	2154	0.170	0.38	0.022-0.263
DR Chest compressions	2245	0.088	0.29	0.034-0.200
Pneumothorax	2194	0.066	0.25	0.022-0.155
Death within first 14 days	2247	0.086	0.28	0.039-0.160

Note: The sample includes infants that were born on or after Jan 1, 2002 that have reached status. SD denotes standard deviation.

Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. O'Brien-Fleming[i] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

From: Higgins, Rosemary (NIH/NICHD)
To: Abbot Laptook
Cc: Neil
Subject: RE: SUPPORT DOCUMENT FOR DSMC
Date: Wednesday, March 16, 2005 12:51:00 PM

Hi Abbot
I have discussed the issue of air leak with Neil – we have decided to leave it as solely pneumothorax. PIE is sometimes subjective on a film. Pneumomediastinum is relatively rare in tiny babies without a concurrent pneumothorax. For now, we have decided not to change reporting other than for pneumothoraces. Thanks for your thoughtfulness.
Rose

From: Abbot Laptook [mailto:ALaptook@WIHRI.org]
Sent: Tuesday, March 08, 2005 9:48 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT DOCUMENT FOR DSMC

Rose
One comment; the issue of air leak needs to be defined. Is this solely pneumothorax or does it include PIE and pneumomediastinum. Abbot

---

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, March 03, 2005 4:34 PM
To: Abbot Laptook; Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: 'petrie, carolyn'; 'Betty Hastings'
Subject: SUPPORT DOCUMENT FOR DSMC

HI,
The SUPPORT Subcommittee has finalized a document for assistance with potential trial complications for use by the DSMC. Your comments are welcome. Note that ranges of complications are included for reference or guidance for the NICHD NRN population. Please comment by March 14.
Thanks
Rose

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

From: Neil Finer
To: "Shankaran, Seetha"; Higgins, Rosemary (NIH/NICHD) [E]; mcw3@cwru.edu
Cc: yvaucher@ucsd.edu; "Richard J. Martin"
Subject: RE: SUPPORT secondary
Date: Monday, March 14, 2005 3:14:09 PM

Hi Seetha
As always you make good points. The later evaluation of the infants is currently indicated in the protocol, but there is no method for this evaluation. We are hoping to look at other funding sources for this phase of the ancillary, if it is to be included. If we can bring these infants back for a subsequent study it would be very informative to the question of whether early episodic desaturations predisposes to later disordered breathing.
Richard and I are discussing possible approaches. I will also ask Yvonne Vaucher, our FU PI to be a part of this, and ask Richard to discuss with Maureen Hack at Case.
Regards
Neil

From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Monday, March 14, 2005 10:50 AM
To: Rose; mcw3@cwru.edu; Neil
Subject: SUPPORT secondary

Hi
I read the support secondary re episodes of desaturation

Excellent idea
My suggestions
a) Add a FU PI to protocol since the study does involve FU
b) Will 2 sites be able to enroll all patients?
c) The protocol does mention evaluation of episodes of desaturation at 18-24 months as a measure of disordered breathing. How will this be done? Did I miss something? Will this add to costs Currently only data center costs?

Hope this helps
Seetha

From: Neil Finer
To: "Shankaran, Seetha"; Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Ken"; "Abhik"
Subject: RE: SUPPORT DOCUMENT FOR DSMC
Date: Monday, March 14, 2005 3:09:51 PM

Thanks Seetha
We are trying to provide guidelines for the DSMC, and hope that knowledge of the occurrence of such events would assist them in putting any event into proper context. There is indeed wide variation in the Network, and some have suggested that if the adverse event is increased but not outside the expected occurrence range, that you would give significant consideration to stopping a study on that basis. The Adverse events will be looked at overall, and hopefully a single site would not overweight the statistics.
Neil

From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Monday, March 14, 2005 10:57 AM
To: Higgins, Rosemary (NIH/NICHD)
Cc: Neil; Ken; Abhik
Subject: RE: SUPPORT DOCUMENT FOR DSMC

Rose
Just a couple of questions/clarification by today's deadline for responses.

1) I am concerned that the complications listed occur with a wide range in the 24 to 25 week category between the centers (there is a 10 difference between sites for the same complication/SAE) I know infants will be stratified into the BWT categories at enrollment---what happens if there is an overall imbalance weighting towards more ELBW infants enrolled ? Or a high enrolling site has a high complication/SAE rate?

2) Will SAE be monitored after every 30 infants enrolled (seems a lot of work) or after 30 SAE are reported?

Hope this helps
Seetha

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, March 03, 2005 4:34 PM
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: 'petrie, carolyn'; 'Betty Hastings'
Subject: SUPPORT DOCUMENT FOR DSMC

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> Thanks
> Rose

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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD)
To: Shankaran, Seetha
Cc: Neil; Ken; Abhik
Subject: RE: SUPPORT DOCUMENT FOR DSMC
Date: Monday, March 14, 2005 2:29:00 PM

Seetha
The ranges are included as a guide for the DSMC – there is a wide variation in the incidence of complication at various sites. The DSMC would make recommendations based on the information that they receive.

The serious adverse events are closely monitored; the groups will be assessed by the data center on an ongoing basis. Yes, it is a lot of work, but appropriate to follow this trial.

Thanks
Rose

From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Monday, March 14, 2005 1:57 PM
To: Higgins, Rosemary (NIH/NICHD)
Cc: Neil; Ken; Abhik
Subject: RE: SUPPORT DOCUMENT FOR DSMC

Rose
Just a couple of questions/clarification by today's deadline for responses.

1) I am concerned that the complications listed occur with a wide range in the 24 to 25 week category between the centers (there is a 10 difference between sites for the same complication/SAE) I know infants will be stratified into the BWT categories at enrollment---what happens if there is an overall imbalance weighting towards more ELBW infants enrolled ? Or a high enrolling site has a high complication/SAE rate?

2) Will SAE be monitored after every 30 infants enrolled (seems a lot of work) or after 30 SAE are reported?

Hope this helps
Seetha

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, March 03, 2005 4:34 PM
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: 'petrie, carolyn'; 'Betty Hastings'
Subject: SUPPORT DOCUMENT FOR DSMC

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The SUPPORT Subcommittee has finalized a document for assistance with potential trial complications for use by the DSMC. Your comments are welcome. Note that ranges of complications are included for reference or guidance for the NICHD NRN population. Please

comment by March 14.
Thanks
Rose

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higginsr@mail.nih.gov

From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Neil Finer
Subject: RE: Miami IRB for SUPPORT - follow up
Date: Monday, March 14, 2005 10:20:08 AM

OK
Shahnaz

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 14, 2005 8:43 AM
To: Neil Finer; Duara, Shahnaz
Cc: Rosemary Higgins
Subject: RE: Miami IRB for SUPPORT - follow up

Neil and Shahnaz, I will call the FDA today to get some information.
Thanks Rose

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Saturday, March 12, 2005 1:41 PM
To: Duara, Shahnaz
Cc: Rosemary Higgins; Higgins, Rosemary (NIH/NICHD)
Subject: Re: Miami IRB for SUPPORT - follow up

Thanks Shahnaz
Rose do you want to also discuss with FDA?
Neil
----- Original Message -----
From: "Duara, Shahnaz" <SDuara@med.miami.edu>
To: "Rosemary Higgins" <HIGGINSR1@gunet.georgetown.edu>; "Neil Finer" <nfiner@ucsd.edu>
Sent: Wednesday, March 09, 2005 3:55 PM
Subject: Miami IRB for SUPPORT - follow up

Hi,

Latest news - Owen Reese of WIRB called a little while ago to say that the FDA told them that the oximeter change that Masimo made was probably OK but for them to give formal clearance, they would need to review the protocol.

With this response, Owen Reese gave me 2 options:

1. Submit protocol to the FDA - risk them turning it down
2. Submit the protocol to WIRB for review - risk them turning it down because they consider the oximeter change to be a major risk.

Needless to say, I chose #2, which means we are moving forward without any immediate need to go to the FDA.

Keeping my fingers crossed.

Shahnaz

From: Neil Finer
To: wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.; Michele Walsh-Sukys; dale_phelps@urmc.rochester.edu
Subject: Re: SUPPORT DOCUMENT FOR DSMC
Date: Saturday, March 12, 2005 9:25:43 PM

Hi Rose
We were trying to select outcomes that we postulated would be greater with either of the therapies - we have no data to suspect that NEC/Isolated Perf are increased with CPAP vs M Vent or low vs hi sat. In our study of comparing synchronous nasal IMV versus other modalities we found an increase only for NEC in the nasal SIMV vs the other modalities. I would keep these safety endpoints as few as possible and potentially relevant.
I have copied the committee - please weigh in if you have any comments
Neil

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: 'Neil Finer ' ; wrich@ucsd.edu
Sent: Friday, March 11, 2005 8:12 AM
Subject: FW: SUPPORT DOCUMENT FOR DSMC

Thoughts on NEC, isolated perf??

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Friday, March 11, 2005 10:52 AM
To: Higgins, Rosemary (NIH/NICHD); Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: 'petrie, carolyn'; 'Betty Hastings'
Subject: RE: SUPPORT DOCUMENT FOR DSMC

Hi Rose,
I've looked this excellent piece over (and thank you, I will use/modify it for Inositol).

I think we should, however, add NEC and Isolated GI perforation to the listing.
They both may be influenced by circulation/perfusion events, and isolated perf does usually occur within the first 14 days.

Dale

Dale L. Phelps, MD

Professor of Pediatrics and Ophthalmology

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, March 03, 2005 4:34 PM
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Phelps, Dale; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)

Cc: 'petrie, carolyn'; 'Betty Hastings'
Subject: SUPPORT DOCUMENT FOR DSMC

HI,
The SUPPORT Subcommittee has finalized a document for assistance with potential trial complications for use by the DSMC. Your comments are welcome. Note that ranges of complications are included for reference or guidance for the NICHD NRN population. Please comment by March 14.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Phelps, Dale
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Neil Finer, MD"; "Ken Poole, PhD"
Subject: RE: Secondary Study to SUPPORT
Date: Friday, March 11, 2005 11:54:28 AM

Hi Rose,
This is a very interesting secondary and I'm delighted to vote "yes" on it.

However, the data analysis may be more complex than anticipated, even by this experienced group.

The definition of a desaturation episode as a fall by 10% (presumably absolute 10%, not relative 10%) is creative and addresses the problem of starting from different baselines (we hope they are different).

The protocol does not address how 'artifacts' are going to be defined or dealt with. These are frequent (although hopefully far less frequent with the SET technology than we in STOP-ROP had with the Ohmeda technology). In the STOP-ROP data set, we have repeatedly bogged down trying to do such analyses. Surprisingly, at the time we came closest to what we thought was 'are apneas more frequent in the lower saturation group?' the answer was no.

I strongly urge that some actually planned analyses of actual tracings be done very early on in these collections. In STOP-ROP, it used to take us an overnight run on the computer to analyze the data from one infant for the first two weeks. (we downloaded the first two weeks on each infant). (of course computers are faster now. :-) You may find you need more time at RTI than expected.

Dale Phelps

> -----Original Message-----
> **From:** Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> **Sent:** Monday, March 07, 2005 4:20 PM
> **To:** Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Phelps, Dale; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
> **Cc:** Petrie, Carolyn; bkh@rti.org
> **Subject:**
>
> HI,
> Attached is a SUPPORT secondary study to be conducted at two sites (UCSD and CWRU). There are NO additional costs (other than data center) to do this study. Please end me a yes/no vote by March 14, 2005.
> Thanks
> Rose
>
> Rosemary D. Higgins, M.D.
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine
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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD)
To: Stevens, Timothy
Cc: Phelps, Dale
Subject: Reviews for secondary study
Date: Friday, March 11, 2005 10:07:00 AM
Attachments: ad board #1.doc
ad board #2.doc
ad board#3.doc
Outside Review #1.doc
Outside reviewer #2.DOC

Hi Tim,
I have attached the reviews for the secondary pulmonary outcomes study. I will put this study on the list for the PI budget vote. Thanks for all the hard work.

Let me know if you have any questions.
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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I don't have many comments-- the protocol seems to be well conceived and will probably report useful data. Some minor questions:

1) the questionnaires are 'derived' from the Tucson study. How much were they changed-- was it enough that re-validation (or at least specific
piloting) is needed?

2) I'm a bit concerned about abstracting the charts of the children's primary care physicians. When you just send a request to the physician, even if he/she agrees to do it, there is virtually no control of the accuracy of the abstraction. To me, and to many pediatric epidemiologists, this in fact was a major weakness of the NMIHS follow-up. How confident are the investigators that 1) physicians will cooperate given that $25 is not much money and 2) the data and its abstraction will be reliable and valid.

3) I can't recall if markers of oxidative stress are being collected as part of SUPPORT. If not, should they be?

4) I leave it to others to decide whether the reduction from .29 to .19 in recurrent wheezing with treatment is optimistic

5) Might there be IRB concerns with the central inverview. It's my understanding that in previous studies, the individually identifying information always stayed at the local center. If that's true, might local IRBs and/or parents balk at releasing that information?

6) Questions 18-19 on the follow up questionnaires seem to imply that all full and half-sibs will be living with the study child. This may not be the case, so perhaps these questions need re-visiting.

1) These kids may go to a variety of places for care-- a primary care practice, an ER, acute care center, etc. Will you really be able to get all those charts (of note, I realize that while getting all the charts is probably doable in Rochester, it's a far different world almost anywhere else).

2) Does the questionnaire iscriminate well in ex-preemies (as opposed to a more normal group of children in the Tucson study)? Will parents from the social strata where these children will tend to come from be able to answer the questionnaire.

A much needed - and well thought out study - it may be difficult to dissect the effects of ventilatory style/O2/CO2 and genetics - but certainly worth trying!

I have reviewed both the secondary protocol for pulmonary outcomes and the main trial SUPPORT Protocol. and have the following comments:

Is the question significant? **Yes** Is the question still unresolved? **Yes**

2. What are the strengths and weaknesses of the following design elements:
   a. Primary and secondary outcome measures **Good**
   b. Eligibility, inclusion and exclusion criteria **Good**
   c. Study groups **Well-designed and described**
   d. Assignment **Good**
   e. Masking **Good**
   f. Surveillance for complications **Good (see below with question of monitoring for ROP)**
   g. Follow-up **Good**

General Comments: This a well-designed protocol and addresses an important area affecting the small premature infant of the effects of CPAP and pO2 on morbidity and long term sequelae of chronic lung disease (CLD).

3. Are there other important ancillary protocols (to be done at individual centers)? Should any ancillary project be a part of the primary study? **In addition to measures of pulmonary function, the protocol could evaluate effects of lung immunologic function in the 2 arms of the protocol. For example, what are the characteristics of tracheal aspirates or gentle lung saline washouts? Number of PMNs, content of activated forms of)2 (OH., H2O2, O*), quantity and characteristics of alveolar macrophages (AMs)? These could have implications for susceptibility to infection and long term sequelae of lung damage leading to CLD.**
4. Do you anticipate any other problems with the protocol? M**My only question is whether the arm of the protocol with high pO2 (91-95% O2) is potentially dangerous for development of retinopathy (ROP)? How will this be monitored?**
5. Please comment on the feasibility of the study.

This is a feasible study which should yield important information.

Thanks for the opportunity to review these protocols.

Date: March 10, 2005

TO: Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatal Branch
CDBPM, NICHD, NIH

RE: Support Trial Follow-on Study of Outpatient Pulmonary Outcomes

Dear Dr. Higgins:

In response to your request of the above proposal I offer the following:

1. Is the question significant? Is the question still unresolved?

   Response: Yes to both. Certainly the question(s) are significant. The longer-term impact of what amounts to significant changes in neonatal management of these ELBW babies is probably of greater significance than what happens to them in the NICU. As documented in the proposal, there simply is no controlled, prospective data on either the impact of managing these infants with lower oxygen saturations or on early institution of CPAP.

2. What are the strengths and weaknesses of the following design elements.
   a. Primary and secondary outcome measures.
      Response: As outlined the primary outcome measure is the prevalence of frequent wheezing as documented by parental report via telephone interview. PFT's with tests of reversibility of airways obstruction would be more ideal and more objective but parental reports of wheezing have been shown to have strong correlation with objective measurements. My only concern is that 6 month intervals may be a bit long, risking both losses to follow-up and the vagaries of parental memory (the authors even cite the paper by Harel, et al, that the best recall is within three months). Telephone interviews every three months would double the number of interviews, which would require a commensurate increase in the study budget, but I suspect it would be worth the additional cost. The secondary outcomes are appropriate, several of which are more objective and quantitative (e.g., # doctor's visits) and have the additional advantage that to some extent they can be verified—although if the child is seen at a number of different ED's or doesn't' have a primary pediatrician verifying these visits, hospitalizations, or other secondary outcomes may be more difficult than anticipated.

   b. Eligibility, inclusion and exclusion criteria
      Response: These are pre-determined from the SUPPORT study.

   c. Study Groups
      Response: Again, these are pre-determined from the SUPPORT study.

   d. Assignment
      Response: Pre-determined.

   e. Masking
      Response: One of the beauties of having the study done by (effectively) an outside institution is that there is little chance of breaking the study blind. The design lends itself to easily maintaining blinding.

   f. Surveillance for Complications

Response: This is what the study is actually designed to do—that is, examine what could be considered complications of the SUPPORT study. There is no reason to believe that this study should incur any complications other than the potential to violate patient confidentiality. The U of Rochester would appear to have sufficient safeguards in this arena.

g. Follow-up
Response: The study itself is designed to be a follow-up. I will say that I think it would be of great interest to follow these children longitudinally. Do a significant proportion go on to develop "asthma"? (if so, what is the implication of this finding regarding the etiology of our most common pediatric chronic disease?). The fact that these infants will be neurologically evaluated at 18-24 months as part of the SUPPORT study and the synergy that presents is outstanding.

3. Are there other important ancillary protocols (to be done at individual centers)? Should any ancillary project be a part of the primary study?

Response: While I acknowledge that parental reports are a legitimate means of ascertaining wheezing prevalence, are there centers within the network that are accustomed to doing sophisticated pulmonary function tests in small children? This could be both confirmatory and offer some degree of quantitation of airways' responsiveness.

With regard to any ancillary project being part of the primary study, this "follow-on" study would seem to me to be integral to the primary SUPPORT study.

4. Do you anticipate any problems with the protocol?

Response: No major problems. The protocol is straight-forward and the institution appears to have adequate resources and experience with this type of telephone follow-up interview. That said, contacting patients by telephone is becoming increasingly difficult because of "call-intercept" whereby unidentified numbers are not allowed through and because many people are abandoning land lines to cell phones. It would be very important to obtain cell phone numbers and email addresses from families prior to their discharge from the NICU. I wonder as well if the authors gave any thought to contacting families via email. Finally, it may be wise to contact the family within a month of NICU discharge to simply establish the relationship that will be necessary to accomplish the surveys. Performing the survey every three months would also likely improve the rate of follow-up.

The surveys themselves are simply modified versions of the Tucson questionnaire which have been used in a large number of studies and have been well-validated.

5. Please comment on the feasibility of the study.

Response: Assuming there is adequate funding this study is imminently "doable".

My overall assessment is that the study reasonably well designed, asks and will answer important questions, and that given what I would guess is the considerable expense of doing the SUPPORT study, it would foolish not to do it. As I have suggested, I think that more frequent interviews and earlier contact with the family after NICU discharge would improve the study without adding great expense. The study should certainly be adequately powered, as the authors have nicely demonstrated.

While this isn't rocket science, it asks and will hopefully answer some important questions. These children are in the NICU perhaps 2-4 months, on average, but the survivors may spend the rest of their lives with significant pulmonary compromise. It would seem imperative to know if the proposed interventions in the SUPPORT study had long-term implications!

I appreciate the opportunity to participate in this process.

From: Willson, Douglas F *HS
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NICHD Neonatal research Network Confidential Protocol Review
Date: Thursday, March 10, 2005 5:06:35 PM
Attachments: Higgens Letter.DOC

Dear Rose,

I am attaching a word document that will constitute a formal response to your request. I rather enjoyed doing this, having recently just completed a grant proposal for the use of surfactant in infants w/ respiratory failure from RSV. The proposal included a follow-up aim because so many of these kids end up with significant wheezing in the first year or two after hospitalization--not unlike your prematures (indeed, about 20% of the kids were prematures!).

Not sure I had much profound to say. Seems like a "no-brainer" that the neonatologists would want to see longer-term what effects their interventions had on the pulmonary function of these premature infants. The study should be cheap relative to the SUPPORT study itself (which, incidently, I like as well). I'd be curious to know what the proposed budget for the "follow-on" study was (I'd estimate $250,000).

Sorry for the delay. It's been a little rough around her lately! Hope you are well.

Doug

<<Higgens Letter>>

Douglas F. Willson, MD
Medical Director, PICU and Division of Pediatric Critical Care
University of Virginia Children's Medical Center
UVA Health Sciences System
Box 800386
Charlottesville, VA 22908-0386
Phone: 434-982-1707
Fax: 434-982-3843
Email: dfw4m@virginia.edu

> ----------
> From: Higgins, Rosemary (NIH/NICHD)
> Sent: Thursday, March 10, 2005 9:51 AM
> To: Willson, Douglas F *HS
> Subject: RE: NICHD Neonatal research Network Confidential Protocol Review
>
> Doug
> How about a spring break??
> Thanks
> Rose
>
> -----Original Message-----
> From: Willson, Douglas F *HS [mailto:DFW4M@hscmail.mcc.virginia.edu]
> Sent: Wednesday, March 09, 2005 5:06 PM
> To: Higgins, Rosemary (NIH/NICHD)
> Subject: RE: NICHD Neonatal research Network Confidential Protocol Review
>
> Dear Rose,
> Three weeks of service (including two weekends of call in a row), one
> surfactant chapter, and 3 talks (to be given next week at PALISI) and I'm
> just getting to it now! Promise I will look at it in detail tomorrow and

> get back to you tomorrow (I NEED A VACATION!).
>
> Doug
>
> P.S. How are you?
>
> Douglas F. Willson, MD
> Medical Director, PICU and Division of Pediatric Critical Care
> University of Virginia Children's Medical Center
> UVA Health Sciences System
> Box 800386
> Charlottesville, VA 22908-0386
> Phone: 434-982-1707
> Fax: 434-982-3843
> Email: dfw4m@virginia.edu
>
> > ----------
> > From: Higgins, Rosemary (NIH/NICHD)
> > Sent: Tuesday, March 8, 2005 4:08 PM
> > To: dfw4m@virginia.edu
> > Subject: FW: NICHD Neonatal research Network Confidential Protocol
> Review
> >
> > <<File: Willson Feb 2, 2005.doc>><<File: SUPPORT Follow-on Study 10-1
> (2).doc>><<File: Appendix A.doc>><<File: Appendix B.doc>><<File: Appendix
> C.doc>>
> >
> >
> > HI Doug,
> > Did you have a chance to look at this protocol? Let me know.
> > Thanks
> > Rose
> >
> > -----Original Message-----
> > From: Higgins, Rosemary (NIH/NICHD)
> > Sent: Wednesday, February 02, 2005 4:09 PM
> > To: 'Willson, Douglas F *HS'
> > Subject: RE: NICHD Neonatal research Network Confidential Protocol Review
> >
> > Doug
> > Thanks in advance. Attached is the secondary protocol for pulmonary
> > outcomes and the main trial SUPPORT Protocol. There is a list of
> > instructions. Call me if you have any questions.
> > Rose
> >
> > -----Original Message-----
> > From: Willson, Douglas F *HS [mailto:DFW4M@hscmail.mcc.virginia.edu]
> > Sent: Monday, January 31, 2005 5:52 PM
> > To: Higgins, Rosemary (NIH/NICHD)
> > Subject: RE: NICHD Neonatal research Network Confidential Protocol Review
> >
> > Rose,
> > For you, anything! If need be could I run it by a colleague of mine
> in
> > Pulmonary who may be more expert?
> >
> > Doug

> >
> > Douglas F. Willson, MD
> > Medical Director, PICU and Division of Pediatric Critical Care>
> > University of Virginia Children's Medical Center
> > UVA Health Sciences System
> > Box 800386
> > Charlottesville, VA 22908-0386
> > Phone: 434-982-1707
> > Fax: 434-982-3843
> > Email: dfw4m@virginia.edu
> >
> > > ----------
> > > From: Higgins, Rosemary (NIH/NICHD)
> > > Sent: Monday, January 31, 2005 4:33 PM
> > > To: dfw4m@Virginia.EDU
> > > Subject: NICHD Neonatal research Network Confidential Protocol Review
> > >
> > > Hi Doug,
> > >
> > > Based on your expertise, I am wondering if you could confidentially
> review
> > a protocol for the NICHD Neonatal Research Network titled NICHD SUPPORT
> > Trial Follow-on Study of Outpatient Pulmonary Outcomes? This is a
> secondary
> > study to a main trial to look at pulmonary outcomes in very low birth
> weight
> > infants. Let me know if you could complete a review by February 28 and I
> > can send you instructions and the protocol.
> > >
> > > Thanks in advance!
> > >
> > > Rose
> > >
> > >
> > >
> > > Rosemary D. Higgins, M.D.
> > >
> > > Program Scientist for the Neonatal Research Network
> > >
> > > Pregnancy and Perinatology Branch
> > >
> > > Center for Developmental Biology and Perinatal Medicine
> > >
> > > NICHD, NIH
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> > > 6100 Executive Blvd., Room 4B03B
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> > > Bethesda, MD 20892
> > >
> > > (For overnight delivery, use Rockville, MD 20852)
> > >
> > > 301-435-7909
> > >
> > > 301-496-3790 (FAX)
> > >

> > > higginsr@mail.nih.gov
> > >
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> > >
> >
> >
> >
>
>

Date: March 10, 2005

TO: Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatal Branch
CDBPM, NICHD, NIH

From: Doug Willson, MD
University of Virginia Children's Hospital
Charlottesville, VA 22908

RE: Support Trial Follow-on Study of Outpatient Pulmonary Outcomes

Dear Dr. Higgins:

In response to your request of the above proposal I offer the following:

1. Is the question significant? Is the question still unresolved?

   Response: Yes to both. Certainly the question(s) are significant. The longer-term impact of what amounts to significant changes in neonatal management of these ELBW babies is probably of greater significance than what happens to them in the NICU. As documented in the proposal, there simply is no controlled, prospective data on either the impact of managing these infants with lower oxygen saturations or on early institution of CPAP.

2. What are the strengths and weaknesses of the following design elements.
   a. Primary and secondary outcome measures.
      Response: As outlined the primary outcome measure is the prevalence of frequent wheezing as documented by parental report via telephone interview. PFT's with tests of reversibility of airways obstruction would be more ideal and more objective but parental reports of wheezing have been shown to have strong correlation with objective measurements. My only concern is that 6 month intervals may be a bit long, risking both losses to follow-up and the vagaries of parental memory (the authors even cite the paper by Harel, et al, that the best recall is within three months). Telephone interviews every three months would double the number of interviews, which would require a commensurate increase in the study budget, but I suspect it would be worth the additional cost. The secondary outcomes are appropriate, several of which are more objective and quantitative (e.g., # doctor's visits) and have the additional advantage that to some extent they can be verified—although if the child is seen at a number of different ED's or doesn't' have a primary pediatrician verifying these visits, hospitalizations, or other secondary outcomes may be more difficult than anticipated.

   b. Eligibility, inclusion and exclusion criteria
      Response: These are pre-determined from the SUPPORT study.

   c. Study Groups
      Response: Again, these are pre-determined from the SUPPORT study.

   d. Assignment
      Response: Pre-determined.

   e. Masking

Response: One of the beauties of having the study done by (effectively) an outside institution is that there is little chance of breaking the study blind. The design lends itself to easily maintaining blinding.

f. Surveillance for Complications
Response: This is what the study is actually designed to do—that is, examine what could be considered complications of the SUPPORT study. There is no reason to believe that this study should incur any complications other than the potential to violate patient confidentiality. The U of Rochester would appear to have sufficient safeguards in this arena.

g. Follow-up
Response: The study itself is designed to be a follow-up. I will say that I think it would be of great interest to follow these children longitudinally. Do a significant proportion go on to develop "asthma"? (if so, what is the implication of this finding regarding the etiology of our most common pediatric chronic disease?). The fact that these infants will be neurologically evaluated at 18-24 months as part of the SUPPORT study and the synergy that presents is outstanding.

3. Are there other important ancillary protocols (to be done at individual centers)? Should any ancillary project be a part of the primary study?

Response: While I acknowledge that parental reports are a legitimate means of ascertaining wheezing prevalence, are there centers within the network that are accustomed to doing sophisticated pulmonary function tests in small children? This could be both confirmatory and offer some degree of quantitation of airways' responsiveness.

With regard to any ancillary project being part of the primary study, this "follow-on" study would seem to me to be integral to the primary SUPPORT study.

4. Do you anticipate any problems with the protocol?

Response: No major problems. The protocol is straight-forward and the institution appears to have adequate resources and experience with this type of telephone follow-up interview. That said, contacting patients by telephone is becoming increasingly difficult because of "call-intercept" whereby unidentified numbers are not allowed through and because many people are abandoning land lines to cell phones. It would be very important to obtain cell phone numbers and email addresses from families prior to their discharge from the NICU. I wonder as well if the authors gave any thought to contacting families via email. Finally, it may be wise to contact the family within a month of NICU discharge to simply establish the relationship that will be necessary to accomplish the surveys. Performing the survey every three months would also likely improve the rate of follow-up.

The surveys themselves are simply modified versions of the Tucson questionnaire which have been used in a large number of studies and have been well-validated.

5. Please comment on the feasibility of the study.

Response: Assuming there is adequate funding this study is imminently "doable".

My overall assessment is that the study reasonably well designed, asks and will answer important questions, and that given what I would guess is the considerable expense of doing the SUPPORT study, it would foolish not to do it. As I have suggested, I think that more frequent interviews and earlier contact with the family after NICU discharge would improve the study without adding great expense. The study should certainly be adequately powered, as the authors have nicely demonstrated.

While this isn't rocket science, it asks and will hopefully answer some important questions. These children are in the NICU perhaps 2-4 months, on average, but the survivors may spend the rest of their lives with

significant pulmonary compromise. It would seem imperative to know if the proposed interventions in the SUPPORT study had long-term implications!

I appreciate the opportunity to participate in this process.

Sincerely,

Douglas F. Willson, MD
Division of Pediatric Critical Care
University of Virginia Children's Hospital

From: Wade Rich
To: "Angelita Hensman"
Cc: "Ken Poole"; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Test
Date: Wednesday, March 09, 2005 3:42:19 PM

Angelita,

Wow ! You are good. Excellent recording, and the infant spends 44% in
range! Nice start.

Wade

-----Original Message-----
From: Schaefer, Scott E. [mailto:schaefer@rti.org]
Sent: Wednesday, March 09, 2005 12:28 PM
To: wrich@ucsd.edu
Cc: Schaefer, Scott E.; Poole, W. Kenneth; Das, Abhik
Subject: RE: Test

Hi Wade,

I ran the PulseOx Data file I got from Angelita. It has data from: 02/14/2005 17:30:18 to 03/04/2005 11:29:53.

The readings are every ten seconds. There are some brief gaps in The data:

02/16/2005 20:32:38 skips to 02/16/2005 20:35:36
02/17/2005 01:35:06 skips to 02/17/2005 01:40:07
03/03/2005 13:31:47 skips to 03/03/2005 13:32:06
and then skips to 03/03/2005 13:32:23
then the file finishes at 03/04/2005 11:29:53

The skipped sections are short (minutes or seconds). I guess they could be adjusting the machine.

There are a total of 152,786 readings.

The break down of the compliance of the SP02 readings is:

SAS Variable	Number of Readings	Percent of Time	Description
SPO2RAW1	15050	9.85%	Num Raw SPO2 Readings <85
SPO2RAW2	9091	5.95%	Num Raw SPO2 Readings >=85 and <88
SPO2RAW3	67544	44.20%	Num Raw SPO2 Readings >=88 and <=92
SPO2RAW4	14551	9.52%	Num Raw SPO2 Readings > 92 and <=95
SPO2RAW5	46550	30.47%	Num Raw SPO2 Readings >95

Scott *8-)

-----Original Message-----

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Monday, March 07, 2005 1:35 PM
To: Schaefer, Scott E.
Subject: RE: Test

No, we are not using Profox. Maynard just used both programs to downlaod data and found them
to contain different data. Angelita and everyone else should be using TxtExtract just as
you understood.
Wade

-----Original Message-----
From: Schaefer, Scott E. [mailto:schaefer@rti.org]
Sent: Monday, March 07, 2005 10:01 AM
To: wrich@ucsd.edu
Cc: Schaefer, Scott E.
Subject: RE: Test

OK Wade,

I am confused about the ProFox. Are you guys going to use that with the 2 second data. Angelita was asking me about this and I sent her the TxtExtract program from Masimo do to the download to the Binary File.

Scott *8-)

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Monday, March 07, 2005 12:51 PM
To: Schaefer, Scott E.
Subject: Test

Scott,
I am a bit worried about the oximetry download software. Maynard at Sharp says he sees
different numbers of days using Profox than he does using the system we are using.
When you get the two week dump from Angelita would it be possible to make sure it
is in fact 2 weeks worth of data ? If we have a problem, I would like to nip
it in the proverbial bud.
Wade

Wade Rich, RRT-NPS
Clinical Research Administrator
Division of Neonatology
UCSD Medical Center
200 W Arbor Dr
San Diego, CA 92103-8774
619-543-5375
pgr 290(b) (6)

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT DOCUMENT FOR DSMC
Date: Tuesday, March 08, 2005 6:44:21 PM

Lets use pneumothorax alone as this is the GDB definition
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, March 08, 2005 6:54 AM
To: 'nfiner@ucsd.edu'
Subject: Fw: SUPPORT DOCUMENT FOR DSMC

Should we incliude PIE?
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Abbot Laptook <ALaptook@WIHRI.org>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Tue Mar 08 09:48:07 2005
Subject: RE: SUPPORT DOCUMENT FOR DSMC

Rose
One comment; the issue of air leak needs to be defined. Is this solely pneumothorax or does it include PIE and pneumomediastinum. Abbot

---

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, March 03, 2005 4:34 PM
To: Abbot Laptook; Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: 'petrie, carolyn'; 'Betty Hastings'
Subject: SUPPORT DOCUMENT FOR DSMC

HI,

The SUPPORT Subcommittee has finalized a document for assistance with potential trial complications for use by the DSMC. Your comments are welcome. Note that ranges of complications are included for reference or guidance for the NICHD NRN population. Please comment by March 14.

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From:	Higgins, Rosemary (NIH/NICHD)
To:	Abbot Laptook (alaptook@wihri.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O"Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc:	Petrie, Carolyn; bkh@rti.org
Date:	Monday, March 07, 2005 4:20:00 PM
Attachments:	Martin- Episodic Desaturations - Version 5.doc

HI,
Attached is a SUPPORT secondary study to be conducted at two sites (UCSD and CWRU). There are NO additional costs (other than data center) to do this study. Please end me a yes/no vote by March 14, 2005.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

INCIDENCE AND CONSEQUENCES OF EPISODIC DESATURATION IN PRETERM INFANTS ENROLLED IN THE NICHD NEONATAL NETWORK OXYGEN SATURATION [SUPPORT] STUDY:

A Proposed Secondary Study

Richard J. Martin, M.D., Juliann M. DiFiore, B.S.E.E., Michele C. Walsh, M.D.
[Case Western Reserve University School of Medicine, Cleveland, OH]

Neil Finer, M.D., Wade Rich, R.C.P.T.
[University of California, San Diego, CA]

ABSTRACT:

Episodes of oxygen desaturation, typically a consequence of apnea or hypoventilation, are almost universal in very low birth weight infants. Neither their incidence, nor potential adverse effects on later neurodevelopmental outome or respiratory patterns are known. The NICHD Neonatal Research Network, of which we are a participant, is about to embark on a multicenter trial in which preterm infants of 24-28 weeks' gestation will be randomized to two levels of baseline oxygen saturation. The effect of baseline oxygen saturation on neurodevelopment at 18 months comprises one of several outcome measures in this trial. However, preliminary data suggest that the frequency of episodic desaturation increases at lower baseline oxygen, and that intermittent hypoxemic episodes may have long lasting effects on neural plasticity, manifest as altered respiratory control. As the specially designed software for the pulse oximeters in this trial will not detect brief episodes of desaturation, we are proposing an ancillary study to quantify desaturation episodes during the first month of life and relate them to potential consequences. This ancillary study is being proposed in Cleveland, and another NICHD Network site, and coordinated closely with the Data Coordinating Center. The proposed study will provide a unique opportunity to characterize the incidence of, risk factors for, and significance of, intermittent hypoxemic episodes in preterm infants, an issue of great importance for the well-being of this population.

A. SPECIFIC AIMS:

We seek to perform a prospective trial at two clinical sites [Cleveland, Univ. CA @ San Diego] involved in the SUPPORT Trial to identify the incidence and consequences of intermittent hypoxemic episodes in preterm infants of 24-28 weeks' gestation. Three sub-aims are proposed:

1. To characterize and compare the incidence and magnitude of episodic desaturation episodes in infants enrolled to the different arms [high vs low baseline oxygen saturation] of the SUPPORT Trial.

2. To correlate the incidence and magnitude of such desaturation episodes over the first month of life with neurodevelopmental outcome at 18-22 months.

3. To correlate the incidence and magnitude of episodic desaturation episodes over the first month with the incidence of subsequent desaturation episodes at 18-22 months as a measure of sleep disordered breathing in early infancy.

B. HYPOTHESES TO BE TESTED:

1. Frequency of episodic desaturation in the neonatal period is increased at lower baseline oxygen saturation.

2. Higher incidence of episodic desaturation in neonates is associated with greater neurodevelopmental handicap at 18-22 months.

3. Higher incidence of episodic desaturation in neonates is associated with greater sleep disordered breathing [manifest by persistent episodes of desaturation] at 18-22 months.

C. RATIONALE:

The SUPPORT Trial will randomize infants to two ranges of SpO_2 in order to test the hypothesis that use of a lower SpO_2 range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity [ROP] and/or the need for surgical intervention. However, the potential risk of a lower SpO_2 range in increasing the incidence of episodic desaturation is unknown. In addition, although the SUPPORT Trial is documenting the total time spent below various levels of SaO_2, prior studies in animal models have suggested that the neural effects of intermittent or episodic hypoxia may differ greatly than those of sustained hypoxia [see below: *Consequences of Episodic Desaturation on Respiratory Control*]. **Therefore, this study represents a unique opportunity to acquire additional data to characterize the safety and consequences of episodic desaturation in a large cohort of preterm infants.**

D. BACKGROUND:

1. Incidence and causes of episodic desaturation:

   Desaturation episodes are ubiquitous in preterm infants, both ventilated and spontaneously breathing. Nonetheless, the precise incidence of these events is not well documented. They are thought to be a consequence of immature respiratory control and aggravated by underlying lung disease [typically bronchopulmonary dysplasia (BPD)]. During assisted ventilation these episodes are secondary to hypoventilation or ineffective ventilation. They may be aggravated by loss of functional residual capacity [FRC] associated with recruitment of abdominal muscles during expiration [Bolivar '95]. This, in turn, may decrease the effectiveness of spontaneous ventilatory efforts [Dimaguila '97], especially in ventilated infants with BPD [Durand '92] and during alert states rather than active or quiet sleep states [Lehtonen '03].

   During the transition from assisted ventilation through continuous positive airway pressure [CPAP] to spontaneous breathing, there are minimal data on the incidence of such events. We speculate that the incidence of episodic desaturation [e.g., a fall in SaO_2 of 10%] would be greater at lower baseline SaO_2. Although this is not clearly documented in neonates, it is known that supplemental oxygen decreases apnea and periodic breathing. In addition, the slight improvement is SaO_2 associated with prone positioning does decrease intermittent hypoxemia [McEvoy '97].

2. Consequences of Episodic Desaturation on Neurodevelopmental Outcome:

   There are limited clinical data on the potential consequences of episodic desaturation in

preterm infants [Martin & Fanaroff '98]. Taylor ['98] observed that, in addition to severe cerebral ultrasound abnormality and BPD, a history of apnea of prematurity was predictive of later impairment of neurodevelopmental outcome. Data from the CHIME Study demonstrate that cardiorespiratory events in the home are associated with a five-point lower mental development index at 12 months [Hunt '04]. These studies have all focused on apnea rather than the accompanying hypoxemic events. The only study to address the latter issue is the observation that mean oximetry desaturation during documented apnea has been shown to predict motor scores at outcome [Cheung '99]. There is also the consistent observation that presence of BPD contributes to a poorer neurodevelopmental outcome in virtually all available trials [Hack '00]. It is possible that the higher incidence of desaturation episodes in these infants with BPD [Durand '92] contributes to the adverse effect of BPD on neurodevelopmental outcome.

3. Consequences of Episodic Desaturation on Respiratory Control:
There is great emerging interest in the field of respiratory neurobiology on the long term consequences of intermittent or episodic hypoxia. **Available data indicate the biologic consequences of intermittent hypoxia may differ greatly to those of sustained hypoxia.** Several groups working independently have provided evidence in immature and mature rats that intermittent, but not sustained, hypoxia provides long-lasting changes in neural plasticity. This is manifest primarily as long-term facilitation of carotid body sensory activity, and it has been proposed that such intermittent hypoxia-induced respiratory plasticity may create selective vulnerability to hypoxia during development [Peng '03, Gozal '03, Mitchell '01]. In the developing rat brain, age at time of exposure to intermittent hypoxia [as well as duration of exposures] affect cortical and hippocampal vulnerability as measured by apoptosis [Gozal '01]. Ancillary imaging studies [e.g., MRI] focused on the brain stem may provide a novel correlation with frequency of episodic desaturation.

During the transition of neonates to childhood, there are very limited data on either the incidence or consequence of episodic desaturation. Healthy two-year olds do exhibit some desaturation episodes [Poets '93] and a history of preterm birth increases the odds of sleep disordered breathing in 8 to 11 year olds [Rosen '03]. Finally, preterm infants with persistent apnea of prematurity appear to exhibit enhanced hypoxic ventilatory responses, suggesting that a history of prior desaturation episodes may influence respiratory control mechanisms and stability in this population [Nock '04]. Therefore, it is proposed [Hypothesis #3] that a measure of the incidence of episodic desaturation be obtained as a measure of respiratory instability at 18-24 months follow-up of this cohort.

E. METHODOLOGIC ISSUES:

1. Oximetry Sampling:
The infants will be monitored over a period of four to eight weeks, regardless of the need for supplemental oxygen and/or ventilator support. At this time they will have achieved a postconceptional age of 32 weeks. Oximetry data will be acquired utilizing ProFox® software as a means of downloading data from the Masimo® and for further analysis. We propose that desaturation be defined as a fall in SaO_2 >10% from baseline. Other data

[much of which is being collected for the SUPPORT Trial] includes mean lowest saturation during desaturation episodes, mean SaO_2 during entire monitoring period, time <90%, <85%, <80%, <70%, and total number of desaturation episodes.

Episodes of desaturation can occur rapidly and may last for a short duration, therefore, a relatively short averaging time [Farre '98] sample rate are needed for accurate detection. We are currently generating preliminary data to establish an adequate sample rate and averaging time. This will probably result in some adjustment of these parameters as currently proposed in the SUPPORT Trial.
This proposal will require that the infants enrolled in the collaborating centers for this secondary will acquire the oximetry data at 1 sample every 2 seconds as opposed to 1 sample every 10 seconds. This will require a weekly download as opposed to a monthly download. The data will be forwarded to RTI and the data converted to 1 sample every 10 seconds for the main SUPPORT data base. We will work closely with the Research Triangle Institute [RTI] in resolving these details.

2. Sample Size:
Based on prior data [Cheung '99] using a sample of 63 infants, birthweight 750-999 grams, the correlation between mean desaturation secondary to apnea and Bayley Mental Score was estimated to be 0.25. A sample of 123 infants is needed to provide 80% power to detect a correlation of this magnitude [$\forall$ = .05, 2-sided test]. Using previously recorded data from 12 hour overnight cardiorespiratory monitoring studies in 13 preterm infants, the correlation between baseline SaO_2 and the number of desaturations was estimated to be 0.23. A sample of 140 infants is needed to provide 80% power to detect an effect of this magnitude [= .05, 2-sided test]. To account for loss to follow-up, we will inflate the sample by 20% to 168. Confirmation of this sample size will utilize data collected during the pilot phase in Cleveland.

3. Statistical Analysis:
Statistical analysis will include linear regression to assess the univariate relationship between continuous variables, such as the relationship between the number of desaturation episodes and mental or motor scores. When examining the relationship between baseline SaO_2 and number of desaturation episodes, we will have multiple measures per infant, consisting of the baseline SaO_2 and the co-variant number of desaturation episodes. Because multiple pairs of measures on the same infant are correlated, we will use generalized estimating equations [GEE] to analyze periodic desaturation episodes by the baseline SaO_2 over a corresponding time.

F. DISCUSSION OF ANTICIPATED RESULTS:

We anticipate that the low baseline oxygen saturation group will have both an increase in number of desaturation episodes and a greater decrease in oxygen saturation during such episodes when compared to the high baseline group. We speculate that this will be associated with lower mean neurodevelopmental outcome scores at 18-22 months in the low baseline group when compared to the high baseline group.

If there is no difference in the number or severity of desaturation episodes between the low and high baseline oxygen saturation groups we will conclude that keeping the infants in the low baseline oxygen saturation range does not put them at greater risk for episodic desaturation. Even with this finding there will still be variability in the number and severity of desaturation episodes within each group. Therefore, after combining the infants into one group, we anticipate a wide range of desaturation episodes within this group and an association between these episodes and outcome.

We also anticipate an association between the incidence of desaturation episodes in early postnatal life and sleep disordered breathing at 18-22 months. This hypothesis will be tested by comparing low and high oxygen groups if they differ in episodic desaturation, or by pooling the data as above if the two groups do not differ in incidence of desaturation episodes.

A challenge is to attempt to determine whether an association between incidence or severity of episodic desaturation and outcome reflects a causal relationship. Our study design is such that we are targeting one group to have a lower baseline oxygen and [based on preliminary data (Laptook '04)] more episodic desaturation. The two randomized groups by design should be comparable in all other perinatal and neonatal parameters. Therefore, a putative association between outcome and either baseline oxygen or episodic desaturation would suggest a causal relationship. As the SUPPORT Trial will examine the association between baseline saturation and outcome, we believe that additional quantification of the potentially confounding effects of episodic desaturation is essential in order to clarify the mechanism underlying a causal association between baseline oxygen and neurodevelopmental [or respiratory] outcome.

G. BUDGET:

No allocation of funds beyond $10,000 is being requested at this time by the study sites.

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From: Higgins, Rosemary (NIH/NICHD)
To: Raju, Tonse (NIH/NICHD); Spong, Catherine (NIH/NICHD)
Subject: Re: COFN Report for March 2005
Date: Sunday, March 06, 2005 8:14:11 PM

Raju
A few minor things
The number of patients enrolled are as of 1/31/05, not 11/30/04.
SUPPORT has one O, not two.
The oxygen conference is set for Aug 8-9, 2005.
There is no mention of BPCA and RFPs and the notices for comment or upcoming contracts (I think these are called presollicitaion notices). The only wat to really access these things are to go on FEDBIZZOPPS and enter BPCA. I spoke to Anne last week about getting these onto the NICHD RFP link, but I don't think it is consistent. COFN is a good place to tell people about these items as they have a somewhat broader and different audience than the usual RFA page viewers.
Thanks and have fun in Scottsdale!
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Raju, Tonse (NIH/NICHD) <rajut@mail.nih.gov>
To: Spong, Catherine (NIH/NICHD) <spongc@dir49.nichd.nih.gov>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Sun Mar 06 12:08:33 2005
Subject: COFN Report for March 2005

FYI: clearance sheet is on Cathy's table.

Thanks.

Tonse N. K. Raju, MD

Medical Officer/Program Scientist
Pregnancy and Perinatology Branch
CDBPM/NICHD; National Institutes of Health
Bethesda, MD, 20952. Phone: 301-402-1872
Fax 301-496-3790
NIH Homepage:http://www.nih.gov
PPB HOMEPAGE
http://www.nichd.nih.gov/about/cdbpm/pp/pp.htm

From: Higgins, Rosemary (NIH/NICHD)
To: "nfiner@ucsd.edu"
Subject: Re: intubation for surfactant arm
Date: Friday, March 04, 2005 8:03:12 PM

Perhaps a reminder (as opposed to a technical memo) is warranted.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
CC: 'Avroy A. Fanaroff, M.D.' <aaf2@po.cwru.edu>; 'Betty Hastings' <bkh@rti.org>; 'Ed Donovan' <Edward.Donovan@chmcc.org>; 'Ken Poole' <poo@rti.org>; 'Michele' <mcw3@po.cwru.edu>; 'Neil Finer' <nfiner@ucsd.edu>; 'Shahnaz Duara' <sduara@miami.edu>; 'Wade Rich' <wrich@ucsd.edu>
Sent: Fri Mar 04 18:39:38 2005
Subject: RE: intubation for surfactant arm

HI Rose
That would be OK. We should probably reiterate the statements in the manual with an emphasis on the fact that the initial neonatal resuscitation should follow current center standards apart from intubation for surfactant.
Infants randomized to Control/Surfactant must be intubated and receive surfactant within 1 hour, but do not require immediate intubation in the DR.
Please look at this wording and comment
Thanks
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, March 04, 2005 2:53 PM
To: 'nfiner@ucsd.edu'
Subject: Re: intubation for surfactant arm

Maybe we should send a technical memo??

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Fri Mar 04 17:38:25 2005
Subject: RE: intubation for surfactant arm

Agreed

Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, March 04, 2005 1:09 PM
To: Edward Donovan; sduara@miami.edu; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
Cc: Vivek Narendran; Poole, W. Kenneth; Hastings, Betty J.
Subject: RE: intubation for surfactant arm

The protocol state that the control arm "Once stabilized, with received surfactant within 1 hour."

The Manual also says (under section 5.1) for control infants - intubate and give surfactant by 1 hours of age. There does not appear to be an "intubate immediately" directive, so I believe that principles of neonatal resuscitation should be followed as far as PPV, etc.

Let me know if this is not clear - we should make this clear at all the sites.

Rose

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Friday, March 04, 2005 3:58 PM
To: Edward Donovan; Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
Cc: Vivek Narendran
Subject: intubation for surfactant arm

Neil,

I know that we had several phone calls, but, for some reason, it's taken some time to get to the "real question" people in Cincinnati are asking about our first SUPPORT subject who was randomized to early intubation and surfactant.

The question is "when do these subjects need to be intubated?". It is clear that they must be given surf. prior to age 1 hour and therefore need to be intubated prior to one hour. But can they be stabilized first and then intubated?

We teach Cincinnati clinicians to avoid intubating the blue or bradycardic infant. The implication being that, if the infant needs PPV, the PPV should be given by bag and mask until the infant is stable (pink with good HR) and then intubate.

Our fellow interpreted the study protocol to imply that the infant should be intubated first and then "resuscitated" which is not usual care for us.

Does this make sense? In my view, the study design would allow brief

stabilization with bag and mask prior to intubation in the early surfactant group.

Agree?

Thanks,

Ed

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

From: Neil Finer
To: "Edward Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; sduara@miami.edu; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu
Cc: "Vivek Narendran"; wrich@ucsd.edu
Subject: RE: intubation for surfactant arm
Date: Friday, March 04, 2005 4:40:06 PM

HI ED

The intent of this protocol is to allow stabilization as would represent current practice and then to ensure that the infant is intubated and receives surfactant within 1 hour. There is no mandate that the intubation need be done immediately and I personally from our DR research believe that this is not a desirable practice. We stabilize and if the infant is randomized to receive surfactant, will intubate usually within 10 minutes to deliver the surfactant. It is quite acceptable to stabilize, even with CPAP etc as long as the surf is given within 1 hour. This I hour was requested as some sites had indicated that because of their geography and activity it would be impossible to do this sooner. In addition one may give the surf in the NICU if this can be done within the 1 hour time period.

Resuscitation for all infants should represent the Standard of care – including the decision to intubate for resuscitation in a CPAP infant. The timing of the intubation for the Control infants is < 1 hour with no requirement that such an intubation should preclude the standard resuscitation interventions as practiced at that institution

All of my resuscitation research has convinced me that attempting to intubate a ELBW infant with poor lung expansion and bradycardia may lead to further deterioration, and we encourage all approaches to establish adequate lung volume and stabilization including the use of prolonged inflations before considering intubation.

I think that it is important to clarify this early as other centers may encounter the same interpretation.

Do you think that we need to circulate this or restate this?

Regards

Neil

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Friday, March 04, 2005 12:58 PM
To: Edward Donovan; higginsr@mail.nih.gov; sduara@miami.edu; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
Cc: Vivek Narendran
Subject: intubation for surfactant arm

Neil,
I know that we had several phone calls, but, for some reason, it's taken some time to get to the "real question" people in Cincinnati are asking about our first SUPPORT subject who was randomized to early intubation and surfactant.
The question is "when do these subjects need to be intubated?". It is clear that they must be given surf. prior to age 1 hour and therefore need to be intubated prior to one hour. But can they be stabilized first and then intubated?
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good HR) and then intubate.
Our fellow interpreted the study protocol to imply that the infant should be intubated first and then "resuscitated" which is not usual care for us.
Does this make sense? In my view, the study design would allow brief stabilization with bag and mask prior to intubation in the early surfactant group.
Agree?
Thanks,
Ed

Edward F. Donovan, M.D.
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3333 Burnet Avenue, ML 7014
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Fax 513-636-0171
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From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"
Subject: RE: SUPPORT DOCUMENT FOR DSMC
Date: Friday, March 04, 2005 2:33:38 PM

Hi Rose
We thought about safety issues for the oximetry arm. They are related to too low or too high SpO2 and would probably translate to increased/decreased ROP & CLD and perhaps other issues like NEC - but this is totally speculative. As a result these are truly being evaluated by the primary hypotheses. In addition we have little to postulate as we are using the current alarm limits as used by the Network. The greater concern was about unblinding. We will be monitoring the oximetry dumps on a monthly basis and so will have detailed data as to where the actual range of SpO2 are being maintained - this is quite unique and will let us know if the range appears dangerously low or high. In fact the monitoring for the oximetry arm is more detailed than the other safety concerns.
So far I am aware of 5 enrolled patients, we have 3, Cincinnati 1, Rhode Island 1. I am aware if 1 pneumo - our baby -doing fine, and the DR CPR we shared yesterday. I did speak to Ed about that baby, and they will file an adverse event, probably study related, but it may not have been.
Looks like we are well started
Regards
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, March 04, 2005 9:30 AM
To: 'nfiner@ucsd.edu'
Subject: Fw: SUPPORT DOCUMENT FOR DSMC

Neil
We focused the document on the DR management - any thoughts on the oxygen arm management issues?
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Phelps, Dale <Dale_Phelps@URMC.Rochester.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Fri Mar 04 12:34:37 2005
Subject: RE: SUPPORT DOCUMENT FOR DSMC

Rose,
Some of the standard deviations in the tables have a problem with some extra periods and spaces
Examples
0..32
0. 34

These things cover the concerns about the DR arm pretty well.

However, I'm not sure there is consideration of the two oxygen arms.... or maybe there is. The real concern about the low arm won't come out until we're looking at the later (18-22 month) outcomes.

By the way, there is an unusual outcome predicted by the Tin data that may be worth DSMC watching. Their 'low oxygen' group had a MUCH lower rate of <10th% at 36 weeks (or maybe it was at the time of discharge home).
:-)

Dale

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, March 03, 2005 4:34 PM
To: Abbot Laptook (alaptook@WIHRI.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Phelps, Dale; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: 'petrie, carolyn'; 'Betty Hastings'
Subject: SUPPORT DOCUMENT FOR DSMC

HI,

The SUPPORT Subcommittee has finalized a document for assistance with potential trial complications for use by the DSMC. Your comments are welcome. Note that ranges of complications are included for reference or guidance for the NICHD NRN population. Please comment by March 14.

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

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301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD)
To: Abbot Laptook (alaptook@wihri.org); Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O"Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (Walid Salhab)
Cc: "petrie, carolyn"; "Betty Hastings"
Subject: SUPPORT DOCUMENT FOR DSMC
Date: Thursday, March 03, 2005 4:33:00 PM
Attachments: 3.3.05 DSMC Monitoring.doc

HI,
The SUPPORT Subcommittee has finalized a document for assistance with potential trial complications for use by the DSMC. Your comments are welcome. Note that ranges of complications are included for reference or guidance for the NICHD NRN population. Please comment by March 14.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial

DATA AND SAFETY MONITORING PLANS

Adverse Events

Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

As background information to help the DSMC monitor this trial, we are providing the following observational data from the network's generic database from January 1, 2002-December 31, 2004. The proportions listed give the overall rate of an adverse event in the network population for each of the gestational age subgroups. The range of proportions for each adverse event across centers is presented to provide an idea about the variation seen over the sites for these outcomes. It is hoped that this information will provide detailed background statistics regarding the population for study in this trial.

It is suggested by the SUPPORT Subcommittee that consideration for a recommendation to stop the trial based on a safety concern would need to involve a statistically significant difference in an adverse event between the treatment groups, and that the occurrence of the adverse event is outside of the limits of plausibility for that specific event according to the most recent Neonatal Research Network data presented below.

Table 1: Overall proportion, variability and ranges across network centers for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	3753	0.237	0.43	0.108-0.371
DR Chest compressions	4050	0.108	0. 31	0.035-0.258
Pneumothorax	3861	0.087	0..29	0.023-0.195
Death within first 14 days	4055	0.159	0.37	0.092-0.325

Table 2: Overall proportion, variability and ranges across network centers for infants with gestational age 24-25 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	1599	0.327	0.47	0.153-0.520
DR Chest compressions	1805	0.133	0. 34	0.029-0.340
Pneumothorax	1667	0.116	0. 32	0.026-0.239
Death within first 14 days	1808	0.249	0.44	0.124-0.485

Table 3: Overall proportion, variability and ranges across network centers for infants with gestational age 26-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	2154	0.170	0.38	0.022-0.263
DR Chest compressions	2245	0.088	0.29	0.034-0.200
Pneumothorax	2194	0.066	0.25	0.022-0.155
Death within first 14 days	2247	0.086	0.28	0.039-0.160

Note: The sample includes infants that were born on or after Jan 1, 2002 that have reached status. SD denotes standard deviation.

Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. O'Brien-Fleming[i] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD) [E]; "Wally Carlo, M.D."; wrich@ucsd.edu; "Everett, Ruth"; edward.donovan@chmcc.org; "Shahnaz Duara"; "Michele Walsh"; "Poole, W. Kenneth"; "Das, Abhik"; "Jobe Alan (E-mail)"
Cc:	"Petrie, Carolyn"; bkh@rti.org
Subject:	RE: SUPPORT DSMC monitoring
Date:	Wednesday, March 02, 2005 3:28:47 PM

I can live with this wording
Thanks Rose
Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, March 02, 2005 9:52 AM
To: Wally Carlo, M.D.; wrich@ucsd.edu; Neil Finer; Everett, Ruth; edward.donovan@chmcc.org; Shahnaz Duara; Michele Walsh; Poole, W. Kenneth; Das, Abhik; Jobe Alan (E-mail)
Cc: Petrie, Carolyn; bkh@rti.org
Subject: SUPPORT DSMC monitoring

Hi,
Attached is a revised document for DSMC monitoring for SUPPORT. We have deleted the 2X SD and 2X SE but have maintained the SD in the table (would include 67% of the population). Please send me final comments by tomorrow afternoon (March 3), so that I can send it to the steering committee on Friday for input and suggestions.
Thanks for all of the thought and effort that has gone into this!!
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD)
To: Wally Carlo, M.D.; wrich@ucsd.edu; Neil Finer; Everett, Ruth; edward.donovan@chmcc.org; Shahnaz Duara; Michele Walsh; Poole, W. Kenneth; Das, Abhik; Jobe Alan (E-mail)
Cc: Petrie, Carolyn; bkh@rti.org
Subject: SUPPORT DSMC monitoring
Date: Wednesday, March 02, 2005 12:52:00 PM
Attachments: 3.2. 05 DSMC Monitoring adrev.doc

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Attached is a revised document for DSMC monitoring for SUPPORT. We have deleted the 2X SD and 2X SE but have maintained the SD in the table (would include 67% of the population). Please send me final comments by tomorrow afternoon (March 3), so that I can send it to the steering committee on Friday for input and suggestions.
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The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial

DATA AND SAFETY MONITORING PLANS

Adverse Events

Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

As background information to help the DSMC monitor this trial, we are providing the following observational data from the network's generic database from January 1, 2002-December 31, 2004. The proportions listed give the overall rate of an adverse event in the network population for each of the gestational age subgroups. The range of proportions for each adverse event across centers is presented to provide an idea about the variation seen over the sites for these outcomes. It is hoped that this information will provide detailed background statistics regarding the population for study in this trial.

It is suggested by the SUPPORT Subcommittee that consideration for a recommendation to stop the trial based on a safety concern would need to involve a statistically significant difference in an adverse event between the treatment groups, and that the occurrence of the adverse event is outside of the limits of plausibility for that specific event according to the most recent Neonatal Research Network data presented below.

Table 1: Overall proportion, variability and ranges across network centers for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	3753	0.237	0.43	0.108-0.371
DR Chest compressions	4050	0.108	0. 31	0.035-0.258
Pneumothorax	3861	0.087	0..29	0.023-0.195
Death within first 14 days	4055	0.159	0.37	0.092-0.325

Table 2: Overall proportion, variability and ranges across network centers for infants with gestational age 24-25 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	1599	0.327	0.47	0.153-0.520
DR Chest compressions	1805	0.133	0. 34	0.029-0.340
Pneumothorax	1667	0.116	0. 32	0.026-0.239
Death within first 14 days	1808	0.249	0.44	0.124-0.485

Table 3: Overall proportion, variability and ranges across network centers for infants with gestational age 26-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	2154	0.170	0.38	0.022-0.263
DR Chest compressions	2245	0.088	0.29	0.034-0.200
Pneumothorax	2194	0.066	0.25	0.022-0.155
Death within first 14 days	2247	0.086	0.28	0.039-0.160

Note: The sample includes infants that were born on or after Jan 1, 2002 that have reached status. SD denotes standard deviation.

Comment [h1]:

Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. O'Brien-Fleming[i] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

From: Higgins, Rosemary (NIH/NICHD)
To: Das, Abhik
Subject: RE: Changes to SUPPORT Document
Date: Wednesday, March 02, 2005 12:41:00 PM

Terrific
I will send it to the subcommittee.
Thanks
Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, March 02, 2005 12:36 PM
To: Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth
Subject: RE: Changes to SUPPORT Document

The numbers look fine.
Thanks

Abhik

> -----Original Message-----
> **From:** Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> **Sent:** Wednesday, March 02, 2005 10:55 AM
> **To:** Poole, W. Kenneth; Das, Abhik
> **Subject:** Changes to SUPPORT Document
>
> Hi Ken and Abhik
> Attached is a version of the DSMC document for support. I recalculated the SD's and took out the SE's. I think it may be more interpretable.
> Let me know if the numbers are accurate and I can resend to the subcommittee.
> Thanks
> Rose
>
> Rosemary D. Higgins, M.D.
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> higginsr@mail.nih.gov

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To: Poole, W. Kenneth; Abhik Das
Subject: Changes to SUPPORT Document
Date: Wednesday, March 02, 2005 10:55:00 AM
Attachments: 3.2. 05 DSMC Monitoring adrev.doc

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From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: 2 28 05 DSMC Monitoring adrev
Date: Tuesday, March 01, 2005 11:56:03 AM

Great -Thanks Rose
----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
To: "Duara, Shahnaz" <SDuara@med.miami.edu>; "Neil Finer" <nfiner@ucsd.edu>; "Abhik Das" <adas@rti.org>; "Everett, Ruth" <REverett@med.miami.edu>; "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>; <wrich@ucsd.edu>; "Michele Walsh" <mcw3@case.edu>; "Poole Kenneth (E-mail)" <poo@rti.org>; <edward.donovan@chmcc.org>; "Jobe Alan (E-mail)" <Jobea0@chmcc.org>
Cc: <petrie@rti.org>; "Hastings, Betty J." <bkh@rti.org>
Sent: Tuesday, March 01, 2005 7:55 AM
Subject: RE: 2 28 05 DSMC Monitoring adrev

> We will provide the information for reference to the DSMC. They can make a
> recommendation but ultimate decision to stop comes from the NICHD director,
> Dr. Alexander.
> Thanks
> Rose
>
> -----Original Message-----
> From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
> Sent: Monday, February 28, 2005 6:18 PM
> To: Neil Finer; Higgins, Rosemary (NIH/NICHD); Abhik Das; Everett, Ruth;
> Carlo Waldemar (E-mail); wrich@ucsd.edu; Michele Walsh; Poole Kenneth
> (E-mail); edward.donovan@chmcc.org; Jobe Alan (E-mail)
> Cc: petrie@rti.org; Hastings, Betty J.
> Subject: RE: 2 28 05 DSMC Monitoring adrev
>
> Hi,
>
> Question - is it implicit in the design that stopping rules apply within
> GA strata? Shouldn't differences between treatment groups in one GA
> strata lead to stoppage for that strata but continution of the study in
> the other? Do the numbers require an all or none position with respect
> to continuation of the study?
>
> Shahnaz
>
> -----Original Message-----
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Monday, February 28, 2005 1:38 PM
> To: Higgins, Rosemary (NIH/NICHD); Abhik Das; Everett, Ruth; Carlo
> Waldemar (E-mail); wrich@ucsd.edu; Duara, Shahnaz; Michele Walsh; Poole
> Kenneth (E-mail); edward.donovan@chmcc.org; Jobe Alan (E-mail)
> Cc: petrie@rti.org; Hastings, Betty J.
> Subject: Re: 2 28 05 DSMC Monitoring adrev
>
>

> Hi Rose
> I made a few changes in yellow.
> Neil
> ----- Original Message -----
> From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
> To: "Abhik Das" <adas@rti.org>; "Neil Finer" <nfiner@ucsd.edu>;
> "Everett, Ruth" <REverett@med.miami.edu>; "Carlo Waldemar (E-mail)"
> <wcarlo@peds.uab.edu>; <wrich@ucsd.edu>; "Duara, Shahnaz"
> <SDuara@med.miami.edu>; "Michele Walsh" <mcw3@case.edu>; "Poole Kenneth
> (E-mail)" <poo@rti.org>; <edward.donovan@chmcc.org>; "Jobe Alan
> (E-mail)" <Jobea0@chmcc.org>
> Cc: <petrie@rti.org>; "Hastings, Betty J." <bkh@rti.org>
> Sent: Monday, February 28, 2005 7:09 AM
> Subject: 2 28 05 DSMC Monitoring adrev
>
>
> > Hi,
> > Last call for changes on the SUPPORT DSMC document. I would like to
> > get
> it
> > to the steering committee by the end of the Week (march 4). Thanks for
>
> > all the input!! Rose
> > <<2 28 05 DSMC Monitoring adrev.doc>>
> >
>

From:	Neil Finer
To:	Owen Reese
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.; Michele Walsh-Sukys
Subject:	Re: Inquiry re SUPPORT trial
Date:	Monday, February 28, 2005 9:26:11 PM

Hello Dr Reese

Thank you for your inquiry on behalf of Dr S Duara and the University of Miami regarding the SUPPORT Trial of the NICHD Neonatal Research Network

I will try to outline our rationale and purpose and approach to the IRBs below

1. The pulse oximeter that will be used in the SUPPORT trial, and a number of other trials using the same methodology was altered by Masimo to the specifications that were produced by the investigators. We required a methodology that would maintain blinding while managing infants at 2 different saturation ranges. I
2. Because of our desire to ensure that all caretakers would be aware of any significant desaturation or high saturation we designed the oximeter algorithm to have a skew between the ranges of 85% and 95%. Within this range the oximeter will read either 3% higher or lower than the actual saturation value.
3. For reasons of patient safety, and concerns that caretakers would want to know if the infant experienced desaturation or high saturation, above and below these values the oximeter was to read normally. This range was also selected as all investigators felt that this was the range of current targets for saturation management in NICUs for infants who be candidates for this trial.
4. We went through a number of design iterations and testing before we developed the final model. Masimo accepted our design input relative the alteration of the displayed value from the real value between the values of 85% and 95%.
5. We then tested the altered oximeters using an IRB approved protocol in five sites, including Miami, during which we placed a normal and altered oximeter on 20 infants and demonstrated that the oximeters did achieve the target design, and most importantly did display normal values as requested at SpO2 values < 85% and > 95%.
6. Masimo tested the altered design to ensure conformity with the parameters and that these oximeters functioned normally in every function apart from the altered readings between 85% and 95%. These monitors alarm normally, and as a result will inform the caretakers when the infants oximeter values violate the alarm limits. We have chosen alarm limits that reflect current practice in the Network sites, and when these monitors alarm they are responding to real, not altered values.
7. It was never the intent to produce the altered oximeter as a new device, and the manufacturer has not designed the alteration. The investigators have produced the alteration paradigm, which Masimo then incorporate and tested, all exclusively for this trial.
8. There is now one other funded trial using the same oximeter which will begin in Australia, the PI is Dr William Tarnow Mordi. Other trials are being initiated in the UK, and Canada and Europe, all using the same oximeter. All the collaborators agreed to a single design for the alteration, and Masimo agreed that they would produce only a single altered oximeter for all these trials. We expect that another American study - Dr C Cole, PI from Harvard Medical School, will also be initiated using the identical device within the nest 6-9 months.
9. Masimo has written a letter confirming that these oximeters will function normally for all functions apart from the altered range between 85% and 95%. We currently have approval from 9 Network Member Human Subjects Committees, including UCSD, and Pending approval at 3 more of the Network sites, as well as previous approvals for the pilot study which evaluated these oximeters.
10. Masimo has been very supportive in performing the alterations and testing the actual functions of these oximeters, and will supply these to the study sites for their costs. They will not be marketing these altered oximeters.

The recently completed BOOST trial performed in many sites in many countries (Askie, L. M.; HendersonSmart, D. J.; Irwig, L., and Simpson, J. M. (Askie LM/Univ Sydney/Queen Elizabeth II Res Inst/Ctr Perinatal Hlth Serv Res/Bldg DO2/Sydney/NSW 2006/AUSTRALIA). Oxygen-saturation targets and outcomes in extremely preterm infants. New England Journal of Medicine. 2003; 349(10):959-967) also utilized an altered oximeter, but the oximeter used in that trial did not return to normal at any SpO2.

I apologize for this rather long winded response, but I hope that this helps you to understand the methodology of this study as well as our belief that we do not require an FDA approval as all sites to date

have considered this device as minimal risk and a functioning oximeter outside of the altered ranges - and these ranges are investigator altered and described in detail in the protocol. All sites have agreed that the alarm limits are consistent with current practice, and thus we are not exposing the enrolled infants to lower or higher SpO2 values without an alarm, than is current practice.
We are satisfied that the altered oximeters do not represent any additional risk to the infants enrolled in this study.
Regards
Neil Finer

----- Original Message -----
From: Owen Reese
To: nfiner@ucsd.edu
Sent: Friday, February 25, 2005 3:50 PM
Subject: Inquiry re SUPPORT trial

Neil N Finer, MD
Director of Neonatology
University of California, San Diego
San Diego, California

Dear Dr. Finer:

I was referred to you by Dr. Rose Higgins, in hopes that you could answer a question regarding the SUPPORT trial. Western Institutional Review Board has been asked to review this protocol on behalf of Dr. Shahnaz Duara at University of Miami. Our Regulatory Department has concerns about the modified pulse oximeter used in this trial. We are aware that Masimo has validated the software changes, however, we believe that the modifications have rendered this a non-approved device. Therefore, to permit its use in this research, we must either conclude that the device is a non-significant risk device or receive information that the FDA has cleared the device for use in this research. As the oximeter is clearly of substantial importance in diagnosis or treating disease and its malfunction could present a serious risk to the health of the subject, it will be difficult to find this a non-significant risk device.

Was this issue ever addressed to the FDA and did you receive clearance for use of the modified device?

Thank you for your help.

Sincerely,
Owen G. Reese, Jr. MD, CIP
Executive Director
Western Institutional Review Board
3535 Seventh Avenue SW
Olympia, WA 98502-5010
Phone: 360-252-2533
Fax: 360-252-2474

From: Neil Finer
To: Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth
Subject: Re: 2 28 05 DSMC Monitoring adrev
Date: Monday, February 28, 2005 9:00:59 PM

Hi Das
This sounds reasonable.
I would still want to know that if stopping is recommended it is for an occurrence outside of our normal experience.
Neil
----- Original Message -----
From: "Das, Abhik" <adas@rti.org>
To: "Neil Finer" <nfiner@ucsd.edu>
Cc: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>; "Poole, W. Kenneth" <poo@rti.org>
Sent: Monday, February 28, 2005 12:44 PM
Subject: RE: 2 28 05 DSMC Monitoring adrev

To address your concern on this point, I had suggested something like "It is suggested by the SUPPORT Subcommittee that consideration for a recommendation to stop the trial based on a safety concern would need to involve ... the occurrence of the adverse event outside of the limits of plausibility for that specific event according to the most recent Neonatal Research Network data presented below". This gives the DSMC the necessary data to look at, and some flexible guidelines ("outside the limits of plausibility for that specific event") without binding them to explicit bounds.

Thanks

Abhik

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, February 28, 2005 3:29 PM
To: Poole, W. Kenneth; Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: Re: 2 28 05 DSMC Monitoring adrev

Hi Ken and Das
My thought was we suggest that there are 2 conditions to stop. 1. We have a significant increase in the adverse event between the groups 2. That the actual incidence of this event is greater than that seen in the normal experience of the Network Thus 2SD would set the limit. Your thoughts? Neil
----- Original Message -----
From: "Poole, W. Kenneth" <poo@rti.org>
To: "Das, Abhik" <adas@rti.org>; "Neil Finer" <nfiner@ucsd.edu>
Cc: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
Sent: Monday, February 28, 2005 10:57 AM
Subject: RE: 2 28 05 DSMC Monitoring adrev

I agree with Abhik. I don't think +-2SD are very useful bounds since they normally contain 95% of the distribution.

-----Original Message-----
From: Das, Abhik
Sent: Monday, February 28, 2005 1:49 PM
To: 'Neil Finer'
Cc: Poole, W. Kenneth; 'Higgins, Rosemary (NIH/NICHD)'
Subject: RE: 2 28 05 DSMC Monitoring adrev

I wonder whether we should expressly stipulate +/- 2*SD here, because for some of these measures, this would cover the whole gamut from 0 to 100%; so wouldn't really help the DSMC!

Thanks

Abhik

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, February 28, 2005 1:38 PM
To: Higgins, Rosemary (NIH/NICHD); Das, Abhik; Everett, Ruth; Carlo Waldemar (E-mail); wrich@ucsd.edu; Duara, Shahnaz; Michele Walsh; Poole, W. Kenneth; edward.donovan@chmcc.org; Jobe Alan (E-mail)
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To: "Abhik Das" <adas@rti.org>; "Neil Finer" <nfiner@ucsd.edu>; "Everett, Ruth" <REverett@med.miami.edu>; "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>; <wrich@ucsd.edu>; "Duara, Shahnaz" <SDuara@med.miami.edu>; "Michele Walsh" <mcw3@case.edu>; "Poole Kenneth (E-mail)" <poo@rti.org>; <edward.donovan@chmcc.org>; "Jobe Alan (E-mail)" <Jobea0@chmcc.org>
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To: Poole, W. Kenneth
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: 2 28 05 DSMC Monitoring adrev
Date: Monday, February 28, 2005 8:58:52 PM

Hi Ken
I would prefer that the p value be p=.001. Stopping is fraught with hazard and we should have strong evidence if we decide to do this. PINO is a very recent example of stopping for perhaps too little significance.
Neil
----- Original Message -----
From: "Poole, W. Kenneth" <poo@rti.org>
To: "Neil Finer" <nfiner@ucsd.edu>
Cc: "Das, Abhik" <adas@rti.org>
Sent: Monday, February 28, 2005 2:38 PM
Subject: RE: 2 28 05 DSMC Monitoring adrev

No problem with two criteria. My point is that the + 2 SD are trivial boundaries that are somewhat independent of sample size. I think one set of boundaries with a judiciously chosen p-value (0.10 ??) is sufficient.

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Mon 2/28/2005 3:29 PM
To: Poole, W. Kenneth; Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: Re: 2 28 05 DSMC Monitoring adrev

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Subject: RE: 2 28 05 DSMC Monitoring adrev

I agree with Abhik. I don't think +-2SD are very useful bounds since they normally contain 95% of the distribution.

-----Original Message-----
From: Das, Abhik
Sent: Monday, February 28, 2005 1:49 PM

To: 'Neil Finer'
Cc: Poole, W. Kenneth; 'Higgins, Rosemary (NIH/NICHD)'
Subject: RE: 2 28 05 DSMC Monitoring adrev

I wonder whether we should expressly stipulate +/- 2*SD here, because for some of these measures, this would cover the whole gamut from 0 to 100%; so wouldn't really help the DSMC!

Thanks

Abhik

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, February 28, 2005 1:38 PM
To: Higgins, Rosemary (NIH/NICHD); Das, Abhik; Everett, Ruth; Carlo Waldemar (E-mail); wrich@ucsd.edu; Duara, Shahnaz; Michele Walsh; Poole, W. Kenneth; edward.donovan@chmcc.org; Jobe Alan (E-mail)
Cc: Petrie, Carolyn; Hastings, Betty J.
Subject: Re: 2 28 05 DSMC Monitoring adrev

Hi Rose
I made a few changes in yellow.
Neil
----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
To: "Abhik Das" <adas@rti.org>; "Neil Finer" <nfiner@ucsd.edu>; "Everett, Ruth" <REverett@med.miami.edu>; "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>; <wrich@ucsd.edu>; "Duara, Shahnaz" <SDuara@med.miami.edu>; "Michele Walsh" <mcw3@case.edu>; "Poole Kenneth (E-mail)" <poo@rti.org>; <edward.donovan@chmcc.org>; "Jobe Alan (E-mail)" <Jobea0@chmcc.org>
Cc: <petrie@rti.org>; "Hastings, Betty J." <bkh@rti.org>
Sent: Monday, February 28, 2005 7:09 AM
Subject: 2 28 05 DSMC Monitoring adrev

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> Hi,
> Last call for changes on the SUPPORT DSMC document. I would like to
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it
> to the steering committee by the end of the Week (march 4). Thanks for
> all the input!! Rose
> <<2 28 05 DSMC Monitoring adrev.doc>>
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From: Neil Finer
To: Duara, Shahnaz; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Everett, Ruth; Carlo Waldemar (E-mail); wrich@ucsd.edu; Michele Walsh; Poole Kenneth (E-mail); edward.donovan@chmcc.org; Jobe Alan (E-mail)
Cc: petrie@rti.org; Hastings, Betty J.
Subject: Re: 2 28 05 DSMC Monitoring adrev
Date: Monday, February 28, 2005 8:55:57 PM

Hi Shahnaz
I would hope that we use strata specific data as in the tables - then we could close an individual arm in a strata if needed.
Neil
----- Original Message -----
From: "Duara, Shahnaz" <SDuara@med.miami.edu>
To: "Neil Finer" <nfiner@ucsd.edu>; "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>; "Abhik Das" <adas@rti.org>; "Everett, Ruth" <REverett@med.miami.edu>; "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>; <wrich@ucsd.edu>; "Michele Walsh" <mcw3@case.edu>; "Poole Kenneth (E-mail)" <poo@rti.org>; <edward.donovan@chmcc.org>; "Jobe Alan (E-mail)" <Jobea0@chmcc.org>
Cc: <petrie@rti.org>; "Hastings, Betty J." <bkh@rti.org>
Sent: Monday, February 28, 2005 3:17 PM
Subject: RE: 2 28 05 DSMC Monitoring adrev

Hi,

Question - is it implicit in the design that stopping rules apply within GA strata? Shouldn't differences between treatment groups in one GA strata lead to stoppage for that strata but continution of the study in the other? Do the numbers require an all or none position with respect to continuation of the study?

Shahnaz

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, February 28, 2005 1:38 PM
To: Higgins, Rosemary (NIH/NICHD); Abhik Das; Everett, Ruth; Carlo Waldemar (E-mail); wrich@ucsd.edu; Duara, Shahnaz; Michele Walsh; Poole Kenneth (E-mail); edward.donovan@chmcc.org; Jobe Alan (E-mail)
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Subject: Re: 2 28 05 DSMC Monitoring adrev

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From: Duara, Shahnaz
To: Neil Finer; Rosemary Higgins
Cc: Michele Walsh-Sukys; Avroy A. Fanaroff, M.D.; Ed Donovan; Duara, Shahnaz; Wally Carlo, M.D.; Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Inquiry re SUPPORT trial
Date: Monday, February 28, 2005 6:26:40 PM

Hi Neil,

Thanks so much for your detailed response. I hope it works. Western IRB, for whom Owen Reese is the Medical Director, is hung up on the issue of Significant Risk Device (which it maintains the altered pulse oximeter is), requiring clearance from the FDA for use in research through an exemption of IDE regulations. I'll keep my fingers crossed for your letter to work.

Shahnaz

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, February 28, 2005 1:57 PM
To: Rosemary Higgins
Cc: Michele Walsh-Sukys; Avroy A. Fanaroff, M.D.; Ed Donovan; Duara, Shahnaz; Wally Carlo, M.D.; Neil Finer; Wade Rich; Rose Higgins
Subject: Fw: Inquiry re SUPPORT trial

Hi Rose and All
I propose sending this to Dr Reese.
Please review and let me know if you want me to send and any changes.
Thanks
Neil
----- Original Message -----
From: Neil Finer
To: wrich@ucsd.edu
Sent: Monday, February 28, 2005 8:42 AM
Subject: Re: Inquiry re SUPPORT trial

Hello Dr Reese
The pulse oximeter that will be used in the SUPPORT trial, and a number of other trials using the same methodology was altered by Masimo to the specifications that were produced by the investigators. We wanted to develop a mechanism of maintaining blinding while managing infants at 2 different saturation ranges. In addition, because of our desire to ensure that all caretakers would be aware of any significant desaturation of high saturation designed the oximeter to have a skew between the ranges of 85% and 95%. Above and below these values the oximeter was to read normally. We went through a number of design iterations and testing before we developed the final model. Masimo accepted our design input relative the alteration of the displayed value from the real value between the values of 85% and 95%. This range was also selected as all investigators felt that this was the range of current targets for saturation management in NICUs for infants who be candidates for this trial.
We then tested the altered oximeters using an IRB approved protocol during which we placed a normal and altered oximeter on 20 infants and demonstrated that the oximeters did achieve the target design, and most importantly did return to normal as requested at < 85% and > 95%.
Masimo tested the altered design to ensure conformity with the parameters and ensure that these oximeters functioned normally in every function apart from the altered readings.
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collaborators agreed to a single design for the alteration, and Masimo agreed that they would produce only a single altered oximeter for all these trials.

Masimo has written a letter confirming that these oximeters will function normally for all functions apart from the altered range between 85% and 95%. We currently have approval from 9 Human Subjects Committees, including UCSD, and Pending approval at 3 more of the Network sites. Masimo has been very supportive in performing the alterations and testing the actual functions of these oximeters, and will supply these to the study sites for their costs. They will not be marketing these altered oximeters.

The recently completed BOOST trial performed in many sites in many countries (Askie, L. M.; HendersonSmart, D. J.; Irwig, L., and Simpson, J. M. (Askie LM/Univ Sydney/Queen Elizabeth II Res Inst/Ctr Perinatal Hlth Serv Res/Bldg DO2/Sydney/NSW 2006/AUSTRALIA). Oxygen-saturation targets and outcomes in extremely preterm infants. New England Journal of Medicine. 2003; 349(10):959-967) also utilized an alterd oximeter, but the oximeter used in that trial did not return to normal at any SpO2.

I apologize for this rather long winded response, but I hope that this helps you to understand the methodology of this study as well as our belief that we do not require an FDA approval as all sites to date have considered this device as minimal risk and a functioning oximeter outside of the altered ranges - and these ranges are investigator altered and described in detail in the protocol. We are satisfied from the extensive testing done to date by ourselves and the manufacturer.

Regards

Neil Finer

----- Original Message -----
From: Owen Reese
To: nfiner@ucsd.edu
Sent: Friday, February 25, 2005 3:50 PM
Subject: Inquiry re SUPPORT trial

Neil N Finer, MD
Director of Neonatology
University of California, San Diego
San Diego, California

Dear Dr. Finer:

I was referred to you by Dr. Rose Higgins, in hopes that you could answer a question regarding the SUPPORT trial. Western Institutional Review Board has been asked to review this protocol on behalf of Dr. Shahnaz Duara at University of Miami. Our Regulatory Department has concerns about the modified pulse oximeter used in this trial. We are aware that Masimo has validated the software changes, however, we believe that the modifications have rendered this a non-approved device. Therefore, to permit its use in this research, we must either conclude that the device is a non-significant risk device or receive information that the FDA has cleared the device for use in this research. As the oximeter is clearly of substantial importance in diagnosis or treating disease and its malfunction could present a serious risk to the health of the subject, it will be difficult to find this a non-significant risk device.

Was this issue ever addressed to the FDA and did you receive clearance for use of the modified device?

Thank you for your help.

Sincerely,
Owen G. Reese, Jr. MD, CIP
Executive Director
Western Institutional Review Board

3535 Seventh Avenue SW
Olympia, WA 98502-5010
Phone: 360-252-2533
Fax: 360-252-2474

From:	Edward Donovan
To:	HIGGINSR1@gunet.georgetown.edu; nfiner@ucsd.edu
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; sduara@miami.edu; WCarlo@PEDS.UAB.EDU; aaf2@po.cwru.edu; mcw3@po.cwru.edu; wrich@ucsd.edu
Subject:	Re: Fw: Inquiry re SUPPORT trial
Date:	Monday, February 28, 2005 4:33:19 PM

Looks good. Wally's additions may be helpful.

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

>>> "Neil Finer" <nfiner@ucsd.edu> 02/28/2005 1:56:31 PM >>>
Hi Rose and All
I propose sending this to Dr Reese.
Please review and let me know if you want me to send and any changes.
Thanks
Neil
----- Original Message -----
From: Neil Finer
To: wrich@ucsd.edu
Sent: Monday, February 28, 2005 8:42 AM
Subject: Re: Inquiry re SUPPORT trial

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Olympia, WA 98502-5010
Phone: 360-252-2533
Fax: 360-252-2474

From: Higgins, Rosemary (NIH/NICHD)
To: "nfiner@ucsd.edu"
Subject: Re: Inquiry re SUPPORT trial
Date: Monday, February 28, 2005 2:23:59 PM

Neil
I think this is fine. I am unsure as to whether or not one should mention that one NRN site uses 80 as the lower sat limit. It may also help to reiterate at the end that the alarm limit of 85 is set such that this poses no significant risk to the baby.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Rosemary Higgins <HIGGINSR1@gunet.georgetown.edu>
CC: Michele Walsh-Sukys <mcw3@po.cwru.edu>; Avroy A. Fanaroff, M.D. <aaf2@po.cwru.edu>; Ed Donovan <Edward.Donovan@cchmc.org>; Shahnaz Duara <sduara@miami.edu>; Wally Carlo, M.D. <WCarlo@PEDS.UAB.EDU>; Neil Finer <nfiner@ucsd.edu>; Wade Rich <wrich@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Mon Feb 28 13:56:31 2005
Subject: Fw: Inquiry re SUPPORT trial

Hi Rose and All
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From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Everett, Ruth; Carlo Waldemar (E-mail); wrich@ucsd.edu; Duara, Shahnaz; Michele Walsh; Poole Kenneth (E-mail); edward.donovan@chmcc.org; Jobe Alan (E-mail)
Cc:	petrie@rti.org; Hastings, Betty J.
Subject:	Re: 2 28 05 DSMC Monitoring adrev
Date:	Monday, February 28, 2005 1:42:22 PM
Attachments:	Stopping Rules Feb 28 2005.doc

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To: "Abhik Das" <adas@rti.org>; "Neil Finer" <nfiner@ucsd.edu>; "Everett, Ruth" <REverett@med.miami.edu>; "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>; <wrich@ucsd.edu>; "Duara, Shahnaz" <SDuara@med.miami.edu>; "Michele Walsh" <mcw3@case.edu>; "Poole Kenneth (E-mail)" <poo@rti.org>; <edward.donovan@chmcc.org>; "Jobe Alan (E-mail)" <Jobea0@chmcc.org>
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The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial

DATA AND SAFETY MONITORING PLANS

Adverse Events

Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

As background information to help the DSMC monitor this trial, we are providing the following observational data from the network's generic database from January 1, 2002-December 31, 2004. The proportions listed give the overall rate of an adverse event in the network population for each of the gestational age subgroups. The range of proportions for each adverse event across centers is presented to provide an idea about the variation seen over the sites for these outcomes. It is hoped that this information will provide detailed background statistics regarding the population for study in this trial.

It is suggested by the SUPPORT Subcommittee that consideration for a recommendation to stop the trial based on a safety concern would need to involve a statistically significant difference in an adverse event between the treatment groups, and that the occurrence of the adverse event is outside of the limits of plausibility for that specific event according to the most recent Neonatal Research Network data presented below. We would suggest that these limits represent the mean occurrence of the event plus or minus 2 Standard Deviations. It should be noted that the mean plus 2 SD would be less than the range of proportion across the centers.

Table 1: Overall proportion, variability and ranges across network centers for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	2 X SE	2 X SD	Range of proportion across centers
IVH grade (3 or 4)	3753	0.237	0.014	0.850	0.108-0.371
DR Chest compressions	4050	0.108	0.010	0.621	0.035-0.258
Pneumothorax	3861	0.087	0.009	0.565	0.023-0.195
Death within first 14 days	4055	0.159	0.011	0.731	0.092-0.325

Table 2: Overall proportion, variability and ranges across network centers for infants with gestational age 24-25 weeks at birth

Variable	N	Proportion	2 X SE	2 X SD	Range of proportion across centers
IVH grade (3 or 4)	1599	0.327	0.023	0.938	0.153-0.520
DR Chest compressions	1805	0.133	0.016	0.679	0.029-0.340
Pneumothorax	1667	0.116	0.016	0.640	0.026-0.239
Death within first 14 days	1808	0.249	0.020	0.865	0.124-0.485

Table 3: Overall proportion, variability and ranges across network centers for infants with gestational age 26-27 weeks at birth

Variable	N	Proportion	2 X SE	2 X SD	Range of proportion across centers
IVH grade (3 or 4)	2154	0.170	0.016	0.751	0.022-0.263
DR Chest compressions	2245	0.088	0.012	0.567	0.034-0.200
Pneumothorax	2194	0.066	0.011	0.495	0.022-0.155
Death within first 14 days	2247	0.086	0.012	0.562	0.039-0.160

Note: The sample includes infants that were born on or after Jan 1, 2002 that have reached status. SE denotes standard error, and SD denotes standard deviation.

Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. O'Brien-Fleming[i] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock[ii] boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

Comment [AD1]: This footnote needs to be filled in or deleted.

Accural Reports

RTI will produce enrollment reports on a monthly basis. This report will consist of Numbers Screened, Numbers Eligible, Numbers Randomized, and Consent Status. This report can be modified as deemed necessary.

From: Higgins, Rosemary (NIH/NICHD)
To: Abhik Das; Neil Finer; Everett, Ruth; Carlo Waldemar (E-mail); wrich@ucsd.edu; Duara, Shahnaz; Michele Walsh; Poole Kenneth (E-mail); edward.donovan@chmcc.org; Jobe Alan (E-mail)
Cc: petrie@rti.org; Hastings, Betty J.
Subject: 2 28 05 DSMC Monitoring adrev
Date: Monday, February 28, 2005 10:09:00 AM
Attachments: 2 28 05 DSMC Monitoring adrev.doc

Hi,
Last call for changes on the SUPPORT DSMC document. I would like to get it to the steering committee by the end of the Week (march 4).
Thanks for all the input!!
Rose

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial

DATA AND SAFETY MONITORING PLANS

Adverse Events

Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

As background information to help the DSMC monitor this trial, we are providing the following observational data from the network's generic database from January 1, 2002-December 31, 2004. The proportions listed give the overall rate of an adverse event in the network population for each of the gestational age subgroups. The range of proportions for each adverse event across centers is presented to provide an idea about the variation seen over the sites for these outcomes. It is hoped that this information will provide detailed background statistics regarding the population for study in this trial.

It is suggested by the SUPPORT Subcommittee that consideration for a recommendation to stop the trial based on a safety concern would need to involve a statistically significant difference in an adverse event between the treatment groups, and that the adverse event is outside of the limits of plausibility for that specific event according to the most recent Neonatal Research Network data presented below.

Table 1: Overall proportion, variability and ranges across network centers for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	2 X SE	2 X SD	Range of proportion across centers
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Table 3: Overall proportion, variability and ranges across network centers for infants with gestational age 26-27 weeks at birth

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Death within first 14 days	2247	0.086	0.012	0.562	0.039-0.160

Note: The sample includes infants that were born on or after Jan 1, 2002 that have reached status. SE denotes standard error, and SD denotes standard deviation.

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RTI will produce enrollment reports on a monthly basis. This report will consist of Numbers Screened, Numbers Eligible, Numbers Randomized, and Consent Status. This report can be modified as deemed necessary.

From: Higgins, Rosemary (NIH/NICHD)
To: "wrich@ucsd.edu"
Cc: "nfiner@ucsd.edu"
Subject: Re: Support and the F - -
Date: Friday, February 25, 2005 6:19:40 PM

It is my understanding that DR.Reese and the Miami IRB feel this is a significant risk device. This represents variability among IRBs. Thus we likely need to comply with the request in order to have the protocol approved.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wade Rich <wrich@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
CC: 'Neil Finer' <nfiner@ucsd.edu>
Sent: Fri Feb 25 18:15:31 2005
Subject: Support and the F - -

Neil, Rose

I spoke with Masimo and since it is an investigator initiated protocol, the Pis and
the local IRB make the decision as to whether it is a significant risk. An oximeter is not
considered a significant risk device by most IRBs.
They were not thrilled with going the the FDA and opening that can of worms.

I would concur.

Wade

Wade Rich, RRT-NPS
Clinical Research Administrator
Division of Neonatology
UCSD Medical Center
200 W Arbor Dr
San Diego, CA 92103-8774
619-543-5375
pgr 290-5230

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; Wade RIch
Cc: Everett, Ruth; sduara@miami.edu
Subject: Re: SUPPORT protocol
Date: Tuesday, February 15, 2005 6:56:06 PM

Hi rose
They have indicated that this device is a current production model in all functions apart from the altered range. They, to our knowledge, did not get special FDA approval, nor did they feel that they needed it. We the investigators have designed the algorithm, and this altered device is not for sale and never will be.
If we need more, we should discuss with them. Our IRB was OK with this, and perhaps a knowledge that many IRBs have approved would help.
Regards
Neil
----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
To: <nfiner@ucsd.edu>; "Wade RIch" <wrich@ucsd.edu>
Cc: "Everett, Ruth" <REverett@med.miami.edu>; <sduara@miami.edu>
Sent: Tuesday, February 15, 2005 12:45 PM
Subject: FW: SUPPORT protocol

> Hi Wade and Neil,
> Did Massimo get any documentation (email, letter) from FDA regarding the use
> of the approved oximeter for use in research so we can assist on the IRB
> issue.
> Thanks
> Rose
>
> -----Original Message-----
> From: Everett, Ruth [mailto:REverett@med.miami.edu]
> Sent: Tuesday, February 15, 2005 3:42 PM
> To: Higgins, Rosemary (NIH/NICHD)
> Subject: FW: SUPPORT protocol
>
> This is the second letter, after I sent the letter form Masimo to her.
>
> _____
>
> From: Cindy Gates [mailto:Cgates@wirb.com]
> Sent: Fri 2/11/2005 4:27 PM
> To: Everett, Ruth
> Cc: sduara@peds.med.maimi.edu; Wayne Roice; Greg Lim
> Subject: RE: SUPPORT protocol
>
>
>
> Dear Ms. Everett:
>
> Thank you for this information. The FDA has specific requirements that must
> be met before devices can be cleared for marketing. The information you

> submitted stated that the FDA number for this model is K992340. However,
> the
> approval information in the FDA files seems to be for the unaltered model
> rather than for the model that will be used in this study. Is there any
> information that the sponsor can provide indicating that this altered
device
> is cleared by the FDA for use in this research?
>
> Thanks,
> Cindy
> -----Original Message-----
> From: Everett, Ruth [mailto:REverett@med.miami.edu]
> Sent: Friday, February 11, 2005 9:10 AM
> To: Cindy Gates
> Cc: sduara@peds.med.maimi.edu
> Subject: SUPPORT protocol
>
>
> Attach is the letter from the Masimo company regarding the changes made to
> the equipment, the modifications does not increase the risk of the infants
> since all of the monitoring will be done in the ranges currently used for
> premature infants 85%-95%. As stated in the study if the baby goes out of
> this range the monitors will respond as usual to alert the staff to make
> decisions as part of the standard protocols used in many intensive care
> units
> throughout the United States and Europe. The objective of this study is to
> make the current usuage range 85% to 95% much tighter, so the currently
used
> range will be limited to a 5% difference rather than a 10% difference from
> the low level range to the high level range.
>
>

From: Das, Abhik
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth
Subject: RE: SUPPORT DSMC Stopping recommendations document
Date: Friday, February 25, 2005 12:54:53 PM

I don't think we are saying that. We will construct Pocock safety bounds for our outcomes, and if there is a difference at p = 0.001 (or something like that, depending on the number of interim looks), then the DSMC may consider stopping (they may consider doing that without looking at any p values at all; it is up to them!). Note that the test statistic constructed for this purpose will use the standard error, not the standard deviation.

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, February 25, 2005 12:48 PM
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth
Subject: RE: SUPPORT DSMC Stopping recommendations document

Does that mean the IVH rate has to be 85% in the experimental group to stop? Wally

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, February 25, 2005 11:46 AM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth
Subject: RE: SUPPORT DSMC Stopping recommendations document

I am not sure I understand your question. If you just want the value, it is 2* square root of (0.24*(1-0.24)) = 0.85.

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, February 25, 2005 12:39 PM
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth
Subject: RE: SUPPORT DSMC Stopping recommendations document

Abhik: Could you us an idea of what the 2 SD for the 24% IVH rate would be? Wally

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, February 25, 2005 11:34 AM
To: Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth
Cc: Wally Carlo, M.D.
Subject: RE: SUPPORT DSMC Stopping recommendations document

SD for a proportion p is simply the square root of p*(1-p), which lies in the range (0,0.5]; so 2*SD would range between (0,1]. It is higher for proportions closer to 0.5 and gets lower for more extreme prevalence rates (very high or very low). Since the rate for IVH is not very extreme in this population (around 24%), the associated 2*SD would be high. As such, the standard error and specially the range across sites

are the more appropriate/useful quantities to look at here.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 25, 2005 11:43 AM
To: Poole, W. Kenneth; Das, Abhik
Cc: 'wcarlo@peds.uab.edu'
Subject: Fw: SUPPORT DSMC Stopping recommendations document

Ken or Ahbik
Can you answer this?
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; nfiner@ucsd.edu <nfiner@ucsd.edu>; wrich@ucsd.edu <wrich@ucsd.edu>; Everett, Ruth <REverett@med.miami.edu>; edward.donovan@chmcc.org <edward.donovan@chmcc.org>; Michele Walsh <mcw3@case.edu>; sduara@miami.edu <sduara@miami.edu>; Poole, W. Kenneth <poo@rti.org>; Das, Abhik <adas@rti.org>; Jobea0@chmcc.org <Jobea0@chmcc.org>
CC: petrie@rti.org <petrie@rti.org>; bkh@rti.org <bkh@rti.org>
Sent: Fri Feb 25 11:40:14 2005
Subject: RE: SUPPORT DSMC Stopping recommendations document

Rose: Looks ok except I do not understand the 2X SD data reaching such high proportions (e.g. 85% for grade 3-4 IVH) or is that 0.85 of 23.7%?
Wally

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 22, 2005 3:39 PM
To: Wally Carlo, M.D.; nfiner@ucsd.edu; wrich@ucsd.edu; Everett, Ruth; edward.donovan@chmcc.org; Michele Walsh; sduara@miami.edu; Poole, W. Kenneth; Das, Abhik; Jobea0@chmcc.org
Cc: petrie@rti.org; bkh@rti.org
Subject: SUPPORT DSMC Stopping recommendations document

Hi SUPPORT Subcommittee,

Attached is a continuing draft of the DSMC rules for SUPPORT. I had received a few comments and have incorporated them. Please comment by Friday, February 25 so that we can send the document to the entire steering committee.

Also, we will need to have a plan for extra oximeters at a few selected sites which I am currently trying to put together.

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth
Subject: RE: SUPPORT DSMC Stopping recommendations document
Date: Wednesday, February 23, 2005 10:14:42 AM
Attachments: 2.22.05 DSMC Monitoring adrev.doc

Here are some suggested changes.
Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 22, 2005 4:39 PM
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; wrich@ucsd.edu; Everett, Ruth; edward.donovan@chmcc.org; Michele Walsh; sduara@miami.edu; Poole, W. Kenneth; Das, Abhik; Jobea0@chmcc.org
Cc: Petrie, Carolyn; Hastings, Betty J.
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Cc:	petrie@rti.org; bkh@rti.org
Subject:	SUPPORT DSMC Stopping recommendations document
Date:	Tuesday, February 22, 2005 4:39:00 PM
Attachments:	2.22.05 DSMC Monitoring.doc

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From: Higgins, Rosemary (NIH/NICHD)
To: Duara, Shahnaz
Subject: RE: SUPPORT
Date: Tuesday, February 15, 2005 4:54:00 PM

I have to put this type of thing through a process. I was hoping that Wade could get something.
Thanks
Rose

-----Original Message-----
From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Tuesday, February 15, 2005 4:53 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT

I will try. Could you send me a generic statement in a separate communication stating that 'since ...., NICHD accepts this altered device for scope of project without needing further regulatory documentation'. That should help. I spent 3 hours yesterday, listening to their presentation to the faculty - they seem to be the ultimate bureaucrats, so the more support (no pun intended) I get from you the better.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 15, 2005 4:45 PM
To: Duara, Shahnaz; Everett, Ruth
Cc: Duara, Shahnaz
Subject: RE: SUPPORT

Shahnaz
Can you try to explain that it is testing saturations levels, show them the graphs, explain that some people use the higher range and some use the lower range as standard in their nurseries, and see what the say? I don't think there was anything from the FDA. The company is not intending to obtain an IDE because they will not market the blinded oximeters. Thanks Rose

-----Original Message-----
From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Tuesday, February 15, 2005 4:42 PM
To: Higgins, Rosemary (NIH/NICHD); Everett, Ruth
Cc: Duara, Shahnaz
Subject: RE: SUPPORT

Thanks - we may need extra funds for psychiatric care to tide us over the new IRB's settling pains

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 15, 2005 4:00 PM
To: Everett, Ruth
Cc: Duara, Shahnaz
Subject: RE: SUPPORT

I am waiting to hear back from Wade - he is checking with the company.
We are testing oximetry levels (in a blinded fashion), not the oximeter.
Thanks Rose

-----Original Message-----
From: Everett, Ruth [mailto:REverett@med.miami.edu]
Sent: Tuesday, February 15, 2005 3:56 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT

Hi Dr. Higgins just to clarify some of the information that I sent to
you earlier. Cindy Gates, RN, JD is a regulatory analyst for the WIRB.

From: Higgins, Rosemary (NIH/NICHD)
To: Everett, Ruth
Subject: RE: FDA/SUPPORT/WIRB
Date: Tuesday, February 15, 2005 3:43:00 PM

I will send Wade and Neil an email to see if they can get something formal through the company regarding communication with FDA.
Thanks
Rose

-----Original Message-----
From: Everett, Ruth [mailto:REverett@med.miami.edu]
Sent: Tuesday, February 15, 2005 3:41 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: FDA/SUPPORT/WIRB

Yes this is the letter, but I think this person is part of the secretary staff and just making sure all of the papers are in. I don't think the content is important, so she persist about the FDA letter. I will forward you her e-mails (2), thanks for your assistance.

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tue 2/15/2005 3:29 PM
To: Everett, Ruth
Cc: Neil Finer (nfiner@ucsd.edu); Wade RIch
Subject: RE: FDA/SUPPORT/WIRB

Hi Ruth,
I am attaching a letter - is this the one you already provided?
Thanks
Rose

-----Original Message-----
From: Everett, Ruth [mailto:REverett@med.miami.edu]
Sent: Tuesday, February 15, 2005 3:26 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: FDA/SUPPORT/WIRB

Hello Dr. Higgins,

Currently , the University of Miami has decided to handle the very large volume of clinical protocols by contracting with an external IRB, called WIRB (Western IRB) for all new protocols. Therefore, the SUPPORT protocol was transferred to this new IRB, and currently it is being reviewed by their staff to make sure all of the necessary paper work is there before it goes to committee. As part of the protocol application process, we had to state who our sponsoring entity was, and give a contact name and number - hence, we have provided them with your information, and you may hear from them directly from time to time.

As part of the initial review process for SUPPORT, one of the internal reviewers noted that we plan to use a medical device that had been FDA approved but altered after approval, and she wanted a letter from the FDA stating that this device has been exempt from further review . I forwarded her the letter we received from Masimo through Wade to submit with our pilot protocol but she still insists on an FDA letter. I am aware of the effort the Network has gone through regarding this part of the study, and I know that if this was our internal IRB reviewing the protocol this would not be a problem. In an effort to clarify the matter I have already contacted Dr Sayer from Masimo regarding this issue and she stated that this device alteration was not submitted to the FDA again for an exempt review because they do not plan to market the device, and it was only altered for this research at the request of the P.I. (Neil Finer) and NICHD. Therefore, I am requesting your advice at this time to see what steps we should take next , and if you could possibly give us a cover letter stating that the agency is satisfied with the minor changes made by Masimo after its monitor was FDA approved, since safety issues are satisfied by the fact that the real values will be used for critical alarms, triggered by values below 85% and above 95% oxygen saturation. I will forward you the e-mail that I received from the WIRB and I will attach the letter we received from Wade (the letter was scanned so it will take a few minutes to appear on your screen).

Thanks

Ruth

(for Dr. Duara)

From: Higgins, Rosemary (NIH/NICHD)
To: bkh@rti.org
Subject: FW: forms
Date: Monday, February 14, 2005 8:28:00 AM
Attachments: 4001.pdf

Baby #1 for SUPPORT!!!

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, February 09, 2005 5:56 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: forms

Rose,

The forms can not be uploaded yet, so I have taken the liberty of scanning you the first form. Whew! This was a bit like birthing an elephant.

Wade

Wade Rich, RRT-NPS
Clinical Research Administrator
Division of Neonatology
UCSD Medical Center
200 W Arbor Dr
San Diego, CA 92103-8774
619-543-5375
pgr 290-(b) (6)

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SUPP02 Rel 1.0
January 4, 2005

Eligibility Form

Center: ___ Site: ___ Network No. ___ Birth No. ___ Mother's Initials: ___ Page 1 of 1

This form should be completed for all inborn infants with a gestational age of 24 0/7 to 27 6/7 weeks gestation by best obstetrical estimates and who are to receive full resuscitation.

A. INCLUSION CRITERIA

1. Inborn infant with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimate? (Y) N
2. Infant to receive full resuscitation as necessary? (Y) N
3. Infant does not have known major congenital malformations? (Y) N

If any of above questions are answered 'N' infant is NOT eligible.

B. EXCLUSION CRITERIA

1. The infant was born during a time when the research apparatus/study personnel are not available? Y (N)

   If Yes, indicate reason: ___

1= Equipment not available	2 = Personnel not available

C. CONSENT

1. Consent Status: 1

0 = Not eligible	4 = Consent not requested
1 = Consent granted	5 = Physician refused consent
2 = Parent unavailable	
3 = Parent refused consent	

a. If parent refused consent (3), consent not requested (4) or physician refused consent (5), indicate reason:

_____

_____

D. RANDOMIZATION

1. Was infant randomized into the study? (Y) N

   If No, indicate reason(s): _____

   If Yes,

   a. Date: [redacted] (b) (6) (Month Day Year) b. Time: 08:30 (Hour Min)

   c. Randomization Number (b) (6)

   d. Treatment Assignment 2

1= Early Extubation and CPAP	2= Early Surfactant and Ventilation

   e. Oximeter Color Code: 2

1= Blue	2= Orange

Initials of person completing this form: BSB

From:	Neil Finer
To:	Michele Walsh-Sukys; Avroy A. Fanaroff, M.D.; Ed Donovan; Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Cc:	Hastings, Betty J.; adas@rti.org
Subject:	Fw: SUPPORT DSMC MONITORING
Date:	Thursday, February 10, 2005 3:37:56 PM
Attachments:	2.9.05 DSMC Monitoring Finer rev Feb 10 05.doc

I'm not sure that this went out. My email is acting up. Here it is (again?)
Neil
----- Original Message -----
From: Neil Finer
To: bkh@rti.org ; adas@rti.org ; Poole, W. Kenneth ; Higgins, Rosemary (NIH/NICHD)
Cc: Michele Walsh-Sukys ; Avroy A. Fanaroff, M.D. ; Ed Donovan ; Shahnaz Duara ; Wally Carlo, M.D. ; Neil Finer ; Wade Rich ; Rose Higgins
Sent: Thursday, February 10, 2005 10:28 AM
Subject: Re: SUPPORT DSMC MONITORING

Hi Everyone
Here is my revision for the stopping rules. Please review and let me and Rose know your thoughts.
Oh yes, one more point, we at San Diego have discovered the cure for preterm labor - its known as the SUPPORT Consent!!. We have now consented 4 women who all but one promptly stopped their labor, should this be another secondary??. We did enroll our first patient.
Be well
Neil

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Poole, W. Kenneth ; Abhik Das (adas@rti.org) ; bkh@rti.org ; Neil Finer (nfiner@ucsd.edu)
Sent: Wednesday, February 09, 2005 12:57 PM
Subject: SUPPORT DSMC MONITORING

Hi,
I have modified the DSMC monitoring plan by incorporating the data provided regarding complication rates of IVH, pneumothorax, DR Chest compression and death for the NRN population. Take a look at it and decided whether or not you believe it is OK for the subcommittee to review, and then go to the steering committee. I did speak with Dr. Berberich at NHLBI regarding inclusion of baseline "complication" rates on average and across sites and she thought this would be important information for the DSMC to have in their possession.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial

DATA AND SAFETY MONITORING PLANS

Adverse Events

Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

These outcomes will be evaluated on a monthly basis by RTI, and if the incidence of any of these outcomes is determined to be ~~5%~~ 10% greater in any arm of the study, this information will be provided to the Study PI and committee and the DSMC for immediate consideration, and evaluated for consideration of termination of the study or treatment arm.

For background information for ~~the convenience of~~ the DSMC, we are providing the following observational data from the network's generic database from Jan 1 , 2002~~.~~ The proportion listed gives the average rate of an adverse event in the population for each of the subgroups. The range of proportions across centers gives the variation seen over the sites. It is hoped that this information will provide detailed background statistics regarding the population for study in this trial.
It would be the suggestion of the SUPPORT Subcommittee that consideration for stopping of this trial would involve a statistical significant increase in an adverse event, and that the actual percent occurrence of that adverse event is outside the limits of 2 Standard Deviations of that event using the current Network data provided below.
As an example, if the IVH rate increased fro 25% to 35% in the 24 to 25 weeks strata, this incidence is within the expected occurrence within this population as 2 Standard Deviations would represent 42%, and we would suggest that the trial not be stopped in this instance.

Table 1: Proportion and 2 Standard Deviations for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	2 X SE	2X SD	Range of proportion across centers
IVH grade (3 or 4)	3753	0.237	0.014	0.850	0.108-0.371
DR Chest compressions	4050	0.108	0.010	0.621	0.035-0.258
Pneumothorax	3861	0.087	0.009	0.565	0.023-0.195
Death within first 14	4055	0.159	0.011	0.731	0.092-0.325

days					

Table 2: Proportion and 2 Standard Deviations for infants with gestational age 24-25 weeks at birth

Variable	N	Proportion	2 X SE	2X SD	Range of proportion across centers
IVH grade (3 or 4)	1599	0.327	0.023	0.938	0.153-0.520
DR Chest compressions	1805	0.133	0.016	0.679	0.029-0.340
Pneumothorax	1667	0.116	0.016	0.640	0.026-0.239
Death within first 14 days	1808	0.249	0.020	0.865	0.124-0.485

Table 3: Proportion and 2 Standard Deviations for infants with gestational age 26-27 weeks at birth

Variable	N	Proportion	2 X SE	2X SD	Range of proportion across centers
IVH grade (3 or 4)	2154	0.170	0.016	0.751	0.022-0.263
DR Chest compressions	2245	0.088	0.012	0.567	0.034-0.200
Pneumothorax	2194	0.066	0.011	0.495	0.022-0.155
Death within first 14 days	2247	0.086	0.012	0.562	0.039-0.160

Note: The sample includes infants that were born on or after Jan 1, 2002 that have reached status.

Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. Obrien-Fleming [i] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock [ii] boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

Accural Reports

RTI will produce enrollment reports on a monthly basis. This report will consist of Numbers Screened, Numbers Eligible, Numbers Randomized, and Consent Status. This report can be modified as deemed necessary.

From: Poole, W. Kenneth
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: RE: SUPPORT DSMC MONITORING
Date: Thursday, February 10, 2005 2:22:09 PM
Attachments: 2.9.05 DSMC Monitoring A.doc

Rose,

There is an inconsistency in the document concerning the stopping rule(s). I suggest deleting the ambiguous statement about 5-10% and going with the revised paragraph under the DSMC monitoring.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 09, 2005 3:57 PM
To: Poole, W. Kenneth; Das, Abhik; Hastings, Betty J.; Neil Finer (nfiner@ucsd.edu)
Subject: SUPPORT DSMC MONITORING

Hi,
I have modified the DSMC monitoring plan by incorporating the data provided regarding complication rates of IVH, pneumothorax, DR Chest compression and death for the NRN population. Take a look at it and decided whether or not you believe it is OK for the subcommittee to review, and then go to the steering committee. I did speak with Dr. Berberich at NHLBI regarding inclusion of baseline "complication" rates on average and across sites and she thought this would be important information for the DSMC to have in their possession.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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The SUPPORT Trial

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These outcomes will be evaluated on a monthly basis by RTI, and if the incidence of any of these outcomes is determined to be 5% - 10% greater in any arm of the study, this information will be provided to the Study PI and committee and the DSMC for immediate consideration, and evaluated for consideration of termination of the study or treatment arm.---Delete

For the convenience of the DSMC, we are providing the following observational data from the network's generic database. The proportion listed gives the average rate of an adverse event in the population for each of the subgroups. The range of proportion across centers gives the variation seen over the sites. It is hoped that this information will provide detailed background statistics regarding the population for study in this trial.

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Variable	N	Proportion	2 X SE	2X SD	Range of proportion across centers
IVH grade (3 or 4)	3753	0.237	0.014	0.850	0.108-0.371
DR Chest compressions	4050	0.108	0.010	0.621	0.035-0.258
Pneumothorax	3861	0.087	0.009	0.565	0.023-0.195
Death within first 14 days	4055	0.159	0.011	0.731	0.092-0.325

Table 2: Proportion and 2 Standard Deviations for infants with gestational age 24-25 weeks at birth

Variable	N	Proportion	2 X SE	2X SD	Range of proportion across centers
IVH grade (3 or 4)	1599	0.327	0.023	0.938	0.153-0.520
DR Chest compressions	1805	0.133	0.016	0.679	0.029-0.340
Pneumothorax	1667	0.116	0.016	0.640	0.026-0.239
Death within first 14 days	1808	0.249	0.020	0.865	0.124-0.485

Table 3: Proportion and 2 Standard Deviations for infants with gestational age 26-27 weeks at birth

Variable	N	Proportion	2 X SE	2X SD	Range of proportion across centers
IVH grade (3 or 4)	2154	0.170	0.016	0.751	0.022-0.263
DR Chest compressions	2245	0.088	0.012	0.567	0.034-0.200
Pneumothorax	2194	0.066	0.011	0.495	0.022-0.155
Death within first 14 days	2247	0.086	0.012	0.562	0.039-0.160

Note: The sample includes infants that were born on or after Jan 1, 2002 that have reached status.

Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. Obrien-Fleming [i] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock [ii] boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. The four adverse events will be monitored individually and in combination. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion. If the adverse event monitoring approaches statistical significance in any arm of the study, this information will be provided to the Study PI, the committee and the DSMC for immediate review, and evaluated for consideration of termination of the study or treatment arm.

Accural Reports

RTI will produce enrollment reports on a monthly basis. This report will consist of Numbers Screened, Numbers Eligible, Numbers Randomized, and Consent Status. This report can be modified as deemed necessary.

From: Higgins, Rosemary (NIH/NICHD)
To: Das, Abhik
Subject: RE: SUPPORT DSMC MONITORING
Date: Wednesday, February 09, 2005 4:26:00 PM

Ok
Thanks
Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, February 09, 2005 4:25 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT DSMC MONITORING

Rose:

When this goes out to the DSMC, we would probably need to define "status" (120 days of age, discharge, transfer or death, whichever comes first), since they may not know what it means.

Thanks

Abhik

> -----Original Message-----
> **From:** Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> **Sent:** Wednesday, February 09, 2005 3:57 PM
> **To:** Poole, W. Kenneth; Das, Abhik; Hastings, Betty J.; Neil Finer (nfiner@ucsd.edu)
> **Subject:** SUPPORT DSMC MONITORING
>
> Hi,
> I have modified the DSMC monitoring plan by incorporating the data provided regarding complication rates of IVH, pneumothorax, DR Chest compression and death for the NRN population. Take a look at it and decided whether or not you believe it is OK for the subcommittee to review, and then go to the steering committee. I did speak with Dr. Berberich at NHLBI regarding inclusion of baseline "complication" rates on average and across sites and she thought this would be important information for the DSMC to have in their possession.
> Thanks
> Rose
>
> Rosemary D. Higgins, M.D.
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine
> NICHD, NIH
> 6100 Executive Blvd., Room 4B03B
> MSC 7510
> Bethesda, MD 20892
> (For overnight delivery, use Rockville, MD 20852)
> 301-435-7909
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD)
To: Poole, W. Kenneth; Abhik Das (adas@rti.org); bkh@rti.org; nfiner@ucsd.edu
Subject: SUPPORT DSMC MONITORING
Date: Wednesday, February 09, 2005 3:57:00 PM
Attachments: 2.9.05 DSMC Monitoring.doc

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From: Rowe, Mona (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; McGrath, John (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Fowler-Lee, Triesta (NIH/NICHD) [E]; Pham, Luan (NIH/NICHD) [E]; Tillman, June (NIH/NICHD) [E]
Subject: RE: Antenatal_Consent_Paper_Network_Revision for Submission Feb 1
Date: Wednesday, February 03, 2010 7:09:39 PM

Thanks for forwarding –just some comments ..hope they may be helpful…look fine to go out –hope you don't mind a few suggestions

Triesta – would go ahead and send to Steve

- Missing some words?

On page 7 .. the sentence

"Mothers receiving a neonatal consult were more likely to consent (p <.001), but consent was obtained during the consult in only 11.6%."

In the sentence above (from above the yellow line on page 7) – are you missing the words after 11.6% …"of the cases" ?

- On the additional paragraph: very minor but the additional words would help clarify for me.

We estimated the cost of the consent process using the data from the questionnaire. Because the time needed to obtain consent was not a continuous variable, the costs were calculated as ranges. It took between 1776 and 3284 hours to enroll 611 infants. Based on the standard coordinator salary for the Network at the time of the trial, the total costs for enrolling these infants represents between $65,513 and $124,822 enrollment costs. Assuming equivalent enrollment for the part of the trial not covered by this secondary study, the total enrollment costs for the trial would have been between $140,852 and $268,367.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, February 02, 2010 11:18 AM
To: Rowe, Mona (NIH/NICHD) [E]; McGrath, John (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: Antenatal_Consent_Paper_Network_Revision for Submission Feb 1

Hi,
Attached is a paper which has already gone through NICHD clearance; there are no NICHD authors on the paper. The SUPPORT study was co-funded by us and NHLBI. The reviewers asked for a cost estimate for the antenatal consent process and the authors have inserted two paragraphs - one in the results and one in the discussion which I have highlighted. Will these be acceptable? Let me know by the

end of this week if this is a problem as the authors want to get the paper back to Pediatrics.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD)
To: Joseph Bellanti
Subject: RE: NICHD Neonatal Research Network Confidential Review
Date: Wednesday, February 02, 2005 4:10:00 PM
Attachments: SUPPORT Follow-on Study 10-1 (2).doc
Appendix A.doc
Appendix B.doc
Appendix C.doc
Support protocol.pdf
Bellanti Feb 2, 2005.doc

Joe
Thanks in advance. Attached is the secondary protocol for pulmonary outcomes and the main trial SUPPORT Protocol. There is a list of instructions. Call me if you have any questions.
Rose

From: Joseph Bellanti [mailto:bellantj@georgetown.edu]
Sent: Monday, January 31, 2005 5:50 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: NICHD Neonatal Research Network Confidential Review

Dear Rosemary:

I would be happy to review the protocol.

Joe

Joseph A. Bellanti, MD
Professor of Pediatrics & Microbiology-Immunology
Director, Immunology Center
Georgetown University Medical Center
3800 Reservoir Road, NW
Washington, DC 20057

tel 202-687-8227
fax 202-784-3597
email bellantj@georgetown.edu

----- Original Message -----
From: higginsr@mail.nih.gov
Date: Monday, January 31, 2005 4:33 pm
Subject: NICHD Neonatal Research Network Confidential Review
>
> The following message was sent to you using the Georgetown
> University directory web site.
> If you have questions about how this email was sent, please see
> http://contact.georgetown.edu/index.cfm?Action=About
> ----------
>
> Hi Joe,
> Based on your expertise, I am wondering if you could

> confidentially review a protocol for the NICHD Neonatal Research
> Network titled NICHD SUPPORT Trial Follow-on Study of Outpatient
> Pulmonary Outcomes? This is a secondary study to a main trial to
> look at pulmonary outcomes in very low birth weight infants. Let
> me know if you could complete a review by February 28 and I can
> send you instructions and the protocol.
> Thanks in advance!
> Rose
> Rosemary D. Higgins, M.D.
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine
> NICHD, NIH
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NICHD SUPPORT Trial Follow-on Study of Outpatient Pulmonary Outcomes

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A. ABSTRACT

Statement of Problem Premature infants have a greater risk for wheezing and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor for later wheezing, the etiology of recurrent wheezing in formerly premature infants is not known.

Hypotheses The goal of the clinical project detailed here is to understand better the antecedents of recurrent wheezing among preterm infants during early childhood by evaluating the effect of treatment with different levels of targeted oxygen saturation in the immediate neonatal period. **The overarching hypothesis is that premature infants exposed to supplemental oxygen suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater symptomatic airway dysfunction when challenged with subsequent environmental or infectious exposures.**

Hypothesis #1- Relative to infants managed with a higher SpO2 range, infants who are managed with a lower targeted SpO2 range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' corrected age (CA) whether they develop CLD or not.

Hypothesis #2- Relative to infants managed with prophylactic surfactant and conventional ventilation, infants who are managed with the early use of CPAP and a permissive ventilator strategy will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' CA whether they develop CLD or not.

Design

Longitudinal follow-up of infants enrolled in the SUPPORT Trial to determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the prevalence of recurrent wheezing and volume of outpatient pulmonary care in the first 18 months' CA.

Definition of outcomes:

A) Parental Report of Wheezing
B) Physician Diagnosed Wheezing.
C) Volume of Outpatient Pulmonary Care including number of pulmonary medications, office and emergency room visits and re-hospitalizations for respiratory illnesses.

Ascertainment of outcomes:

Outcomes will be measured at 4 time points in the first 18-22 months' CA as follows:

1. NICU discharge -baseline interview at to obtain family and environmental history
2. Six months' CA - telephone interview to ascertain prevalence of wheezing and obtain interval history of need for pulmonary care.
3. Twelve months' CA - telephone interview as at 6 months'
4. 18-22 months' CA- Prior to NICHD follow-up clinic visit, a telephone interview to ascertain prevalence of wheezing and obtain interval history of need for pulmonary care will be administered and primary care physician contact information collected for outpatient office chart review.
5. Outpatient chart review- data extraction from patient outpatient medical record.

Anticipated Results

We anticipate that, for infants who develop CLD and those who do not, treatment with a lower vs. higher targeted oxygen saturation range will result in less frequent episodes of wheezing and less need for outpatient pulmonary care in the first 18-22 months' CA.

Benefits and Risks

The proposed SUPPORT Follow-on Pulmonary Outcome Study will directly measure symptomatic airway dysfunction and outpatient pulmonary morbidity in infants treated with either a higher vs. lower targeted oxygen saturation. These data will provide important insight into the effect of different levels of supplemental oxygen exposure on airway growth and development in formerly premature infants. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the neurodevelopmental follow up visit. We anticipate no risk to the patient of this observational follow-on study.

B. STATEMENT OF THE PROBLEM

Premature infants have a greater risk for wheezing and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor for later symptomatic airway dysfunction, the etiology of recurrent wheezing in formerly premature infants is not known.

C. HYPOTHESES

The overarching hypothesis is that premature infants exposed to supplemental oxygen and, to a lesser extent, mechanical ventilation, in the neonatal period suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction and respiratory symptoms when challenged with subsequent environmental or infectious exposures.

Specific Hypotheses:

Hypothesis #1- We hypothesize that relative to infants managed with a higher SpO2 range, infants managed with a lower SpO2 range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care at 18-22 months' CA.

Hypothesis #2- We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

Hypothesis #3- We hypothesize that **among infants with CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

Hypothesis #4- We hypothesize that **among infants without CLD**, infants managed with early use of CPAP and permissive ventilator strategy relative to infants managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

D. SPECIFIC AIMS

The goal of this project is to understand better the etiology of recurrent wheezing among formerly premature infants during early childhood by examining the interaction of oxygen exposure (targeted SpO2 range), surfactant therapy and early nasal CPAP in the newborn period.

SA#1 - Measure the effect of lower vs. higher targeted SpO2 on the prevalence of recurrent wheezing and volume of outpatient pulmonary care among infants born $24^{0/7}$ - $27^{6/7}$ weeks' gestation during the first 18-22 months' CA.

SA#2 - Measure the effect of early CPAP and permissive ventilator strategy compared with prophylactic surfactant and traditional ventilator strategy on the prevalence of recurrent wheezing and volume of outpatient pulmonary care among infants born 24-27 weeks' gestation during the first 18-22 months' CA.

SA#3 – Among infants who develop CLD, determine whether CLD is milder in infants managed with low compared with high targeted SpO2 by measuring recurrent wheezing and volume of outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

SA#4 – Among infants who do not develop CLD, determine whether pulmonary outcome is better for infants managed with a low compared with high targeted SpO2 range by measuring the prevalence of recurrent wheezing and need for outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory

strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

E. RATIONALE/JUSTIFICATION

Although synergy in producing airway injury may exist between oxygen toxicity and mechanical forces applied to the lung, animal and human data suggest that exposure to high concentrations of supplemental oxygen alone is sufficient to cause airway narrowing and greater reactivity to subsequent challenges. Understanding the relative contributions of oxygen toxicity and mechanical forces on airway growth and development may facilitate development of targeted therapies for preventing or reducing symptomatic airway dysfunction in premature infants.

Why measure recurrent wheezing and outpatient pulmonary care as an outcome from a clinical NICU interventional trial?

1) Important information will be available on the effect of oxidant gas exposure on airway development and later symptomatic airway dysfunction. Exposure to oxidant gas has been causally linked with later wheezing. Existing data on the relationship between supplemental oxygen therapy and wheezing come from longitudinal cohort studies, a design that suffers from intrinsic limitations that make controlling for potential confounders of respiratory outcome difficult. By randomizing infants to higher vs. lower target saturation ranges, and thereby presumably higher or lower concentrations of inspired oxygen, *the SUPPORT Trial creates a unique, and perhaps the only, opportunity to evaluate the effect of different levels of supplemental oxygen on subsequent symptomatic airway dysfunction and need for outpatient pulmonary care after NICU discharge.*

2) Using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care can be directly quantified, allowing assessment of whether infants both with and without CLD have improved pulmonary health as a result of the study intervention.

3) The incidence of CLD, defined as an oxygen requirement at 36 weeks' PMA, is an incomplete measure of pulmonary outcome in formerly premature infants during early infancy. CLD as defined above reflects alveolar gas diffusion and NICU oxygen needs. However, outpatient pulmonary morbidity for formerly premature infants is often airway related, involving wheezing either as a primary symptom such as bronchiolitis or as a complicating symptom of lower respiratory tract infection such as pneumonia. The studies proposed here will directly measure the effect of a randomized NICU-based clinical intervention on symptomatic airway dysfunction and outpatient pulmonary morbidity.

4) The risk of a negative trial is reduced. Because the diagnosis of CLD does not completely predict need for outpatient pulmonary care, clinically significant improvements in pulmonary morbidity may occur with minimal or no change in the incidence of CLD. This result has occurred in other interventional trials in which no difference in CLD were observed (12).

5) At present, there is no standard way to measure symptomatic airway dysfunction in premature infants in NICHD pulmonary intervention trials. There is need for a better measure to assess clinical pulmonary outcome to recognize and promote therapies that reduce need for outpatient care of former extremely premature infants.

6) By measuring outpatient pulmonary outcomes, the cost-effectiveness of the SUPPORT study interventions can be assessed. It is reasonable to expect that the SUPPORT Trial interventions will improve outpatient pulmonary outcomes for infants who ultimately develop CLD as well as those who do not. This proposed follow-on study collects the primary data necessary to quantify the cost-effectiveness of this therapy.

F. BACKGROUND / PREVIOUS STUDIES

Recurrent Wheezing In Preterm Infants is a Significant Public Health Problem

Outpatient pulmonary morbidity, especially recurrent wheezing and need for outpatient pulmonary care, is an understudied but clinically important outcome measure for former premature infants with and without CLD. Infants born weighing < 1500 grams (very low birth weight, VLBW) and especially infants born weighing < 1000 grams are at increased risk for small airway narrowing, airway hyperreactivity, wheezing, and nighttime cough (1-11). Up to 30-40% of formerly extremely premature infants have episodes of wheezing after NICU discharge with many requiring bronchodilators and frequent health care visits. Up to 40-50% of premature infants require re-hospitalization, mostly for treatment of respiratory illnesses (9;12;13). In analysis of cross sectional data from the National Maternal Infant Health Survey and 1991 Longitudinal Follow up Survey, the prevalence of asthma-like recurrent wheezing varied markedly with birth weight. Infants with normal birth weight (NBW, > 2500 grams) had a 6.7% prevalence of asthma compared to 10.9% of low birth weight infants (LBW, 1500-2499 grams) and 21.9% for VLBW (14). Mean per capital asthma related costs have been estimated to be 5 times greater for VLBW compared with NBW infants. The net effect is that VLBW infants, who comprise 2% of asthma patients, consume up to 7% of asthma-related therapy costs (14).

Animal Studies

Animal studies suggest that exposure of the premature lung to hyperoxia (without concomitant mechanical ventilation) for relatively brief periods is sufficient to cause airway remodeling and smooth muscle changes that predispose toward airway narrowing and hyperreactivity to subsequent environmental challenges (15-18). In a rhesus monkey model of asthma, Schlegle et al. exposed infant monkeys to repeated cycles of inhaled House Dust Mite Allergen (HDMA), ozone or filtered air. While repeated exposure to either ozone or HDMA had mild effects, exposure to cycles of ozone followed by HDMA resulted in asthma like changes with significant increases in serum IgE, serum histamine, peripheral eosinophilia and greater airway reactivity. Using supplemental oxygen rather than the stronger oxidant ozone, Schulman et al. found that exposure of newborn guinea pigs to 70% oxygen for 96 hours resulted in airway hyperreactivity at 2 and 9 days after the cessation of oxygen. In cell models, intracellular glutathione buffers airway cells against oxidant injury during hyperoxia (19;20). Although the critical period for lung development is comparatively brief in laboratory animals compared with human infants, the duration of hyperoxic exposure (and risk of oxygen toxicity) for treatment of neonatal lung disease may extend for much longer periods in premature infants known to be deficient in anti-oxidant systems such as intracellular glutathione.

Premature Infants <u>With CLD</u> Are At Greatest Risk For Recurrent Wheezing

Among premature infants, infants with bronchopulmonary dysplasia (BPD) are at highest risk for poor pulmonary outcome after NICU discharge. Infants with CLD have small airway compromise with decreased forced expiratory flow velocities, airway hyperreactivity, and increased functional residual volume suggesting airway obstruction (2;5;9;21-24). In a pulmonary follow up of infants with HMD or BPD, De Klein et al. found infants with BPD had reduced FEV1 at baseline while infants with RDS but not BPD had significant improvements in FEV1 following bronchodilator therapy. In this study, a history of recurrent wheezing predicted abnormal pulmonary function (25). In a recent study of infants with CLD, Robin et al. found that 50% of infants with CLD had symptoms of recurrent wheezing and 35% showed significant airway responsiveness to bronchodilators, evidenced by a 24% increase in forced expiratory flow velocity at 75% of expired forced vital capacity (FEF_{75}). This study demonstrated the relationship between recurrent wheezing as a clinical symptom and the physiologic measurement of airway obstruction. Infants with CLD and a history of recurrent wheezing showed greater expiratory flow limitation, hyperinflation, and airway responsiveness to albuterol compared to those without a history of recurrent wheezing (24).

Premature Infants Without CLD Have Significant Airway Dysfunction

Among VLBW infants who do not develop CLD, several studies of pulmonary outcome have found an association between neonatal oxygen exposure and increased prevalence of expiratory flow dysfunction and airway hyperreactivity (4;11;26-29). Some authors attribute reductions in airway function to intrinsically small airways as a consequence of poor intrauterine growth rather than superimposed airway injury or reactivity from neonatal respiratory disease (1;30). However, because small airways alone do not fully explain findings of airway hyperreactivity, other mechanisms of small airway dysfunction are necessary to explain respiratory symptoms.

Several pulmonary outcome studies have reported significant increases (2-fold or more) in airway obstruction among VLBW infants without CLD following exposure to as little as an FIO2 of 0.4 for 5 days (3;4;8;26). Not all studies have had similar results suggesting variability in effect or susceptibility of babies to oxygen exposure (31;32). In 1982, Coates et al. described increased small airway resistance at 10 year follow up of mildly premature infants (mean gestational age 31 weeks and birth weight 2000 grams) treated with a high oxygen (O2) regimen and those exposed to a low O2 regimen for the treatment of respiratory distress syndrome (RDS). Mechanical ventilation was not used in either group. Pulmonary function tests were performed on survivors receiving either the low or high supplemental oxygen regimen ten years after their initial illness. Infants treated with high levels of supplemental oxygen alone (no mechanical ventilation) had decrements in airway function similar to decrements in function reported for a historical cohort of RDS survivors treated with ventilation and high levels of supplemental oxygen. From these data, the authors concluded that neonatal exposure to high oxygen concentrations in the absence of mechanical ventilation is capable of causing long-term change in small airways (28). These studies suggest that use of lower supplemental oxygen concentration may improve respiratory health of infants who do not develop CLD.

Premature Infants Without CLD Have Increased Risk of Recurrent Wheezing and Need for Outpatient Pulmonary Care.

For VLBW infants without CLD, the prevalence of parental or physician reported wheezing is increased compared with term infants, with estimates of the prevalence of wheezing ranging from 10-38% (4;8). Prevalence of wheezing requiring medications is greater compared with term infants. VLBW infants have a 2-4-fold increase in respiratory related re-hospitalization rates compared with term infants (4;8;33-35). Although most studies have found the risk of recurrent wheezing remains elevated throughout childhood, an Australian longitudinal follow-up cohort of VLBW infants found the prevalence of wheezing remained elevated for 2 years then returned to baseline (32;36).

Prevalence of Symptomatic Airway Dysfunction in Formerly Preterm Infants During the Surfactant Era Remains High

With the advent of surfactant therapy, survival for small infants increased dramatically and the incidence of CLD changed minimally (37-40). Classic BPD evolved into the new CLD characterized by reduced alveolarization and more variable airway changes (41). Pulmonary follow up studies during the surfactant era showed reduced pulmonary morbidity in surfactant treated patients. Typical of these studies, Sell et al. found the incidence of asthma was significantly lower in infants given synthetic surfactant compared with those given air placebo. Pelkonen et al. performed PFT measurements on 40 children aged 7-12 years who were born before 30 weeks of gestation with an immature surfactant system, and were randomized to one of three treatment groups: prophylactic surfactant, rescue surfactant and placebo (air). Spirometric parameters of preterm born children were compared with those of 20 children born at term. Bronchial obstruction was found in 53% of the prophylactically treated group, in 36% of the rescue group, in 67% of the placebo group, and in 0% of the control group (42). A recent report suggests that the introduction of surfactant therapy markedly altered the pulmonary outcome of premature infants. Published in 2001, the Newborn Lung Function Project Group reported results of a prospective 12-year follow-up of VLBW infants following the introduction of surfactant therapy. Among infants with CLD, wheezing symptoms decreased from 50 to 16% from the period before compared with the period after surfactant therapy became available. However, among infants without CLD the prevalence of wheezing increased from 14% to 38% with the introduction of surfactant. These data suggest that surfactant therapy has an effect on outpatient respiratory health and underscores the need to

consider outpatient pulmonary outcomes in evaluating therapeutic strategies that potentially decrease surfactant replacement therapy.

CLD is an Incomplete Predictor of Outpatient Pulmonary Morbidity

Several authors have looked to respiratory symptoms and need for outpatient pulmonary care as outcome measures for neonatal lung disease (9;10;12;24). In 1988, from a retrospective chart review of 605 premature infants < 1500 grams, Shennan et al. found that the presence of BPD (oxygen requirement at 36 weeks PMA) had a 63% positive predictive value and a 90% negative predictive value for abnormal pulmonary outcome in the first 2 years of age. However, this study from before the era of exogenous surfactant therapy defined abnormal pulmonary outcome as death, oxygen requirement at 40 weeks PMA, 2 or more respiratory related hospital admissions, wheezing requiring drug therapy or persistent wheezing resulting in growth failure, handicap or hypotonia at 1 year of age. Such restrictive criteria for abnormal pulmonary outcome are likely to underestimate the burden of recurrent wheezing on former premature infants and their families. Several recent interventional studies show that CLD is an incomplete predictor of clinical wheezing and need for outpatient pulmonary care and suggest that differences in oxygen exposure or oxidant stress may affect pulmonary outcome without affecting the incidence of CLD.

Interventional Trials That Did Not Reduce CLD But Did Reduce Outpatient Pulmonary Morbidity.

Recent data in preterm infants treated with human recombinant superoxide dismutase (SOD) found that anti-oxidant therapy did not reduce the incidence of CLD. However, among infants < 27 weeks gestation SOD therapy resulted in significant reductions in the first year after NICU discharge in the number of emergency room visits and number of re-hospitalizations for respiratory problems and reductions in the need for bronchodilators suggesting a reduced prevalence of wheezing in patients treated with SOD (12). In a randomized, multi-center trial from Helsinki, N acetyl cysteine did not reduce the incidence of CLD. Outpatient pulmonary outcome of these patients has not been reported.

Treatment of Premature Infants With Higher Targeted Oxygen Saturations Is Associated with Poorer Pulmonary Outcome

In the STOP-ROP Study, infants exposed to higher levels of oxygen to achieve a targeted saturation of 96-99% compared with 89-94% had greater risk of adverse pulmonary events including pneumonia, chronic lung disease exacerbations and need for diuretics, oxygen and hospitalization at 3 months'' corrected age. *Although all infants in this study had CLD at enrollment, different targeted oxygen saturation were associated with large differences in pulmonary morbidity.* Adverse pulmonary outcomes occurred with differences in FIO2 of as little as 10% for patients treated with ventilation, CPAP or hood (36% $\pm$ 14% vs. 46% $\pm$ 20%, respectively for low vs. high saturation range) and 5% for infants treated with nasal cannula, (26% $\pm$ 6% vs. 31% $\pm$ 11%, respectively for low vs. high saturation range) (44). In a similar study, The Benefits of Oxygen Saturation Targeting (BOOST) Trial randomized infants < 30 weeks' gestation to higher (95-98%) or lower (91-94%) saturations ranges beginning at 32 weeks' PMA to determine whether infants managed with higher targeted saturation range showed better growth and neurodevelopment. As in the STOP-ROP study, need for oxygen therapy was prolonged. Trends towards an increased risk of pulmonary death and fewer outpatient office visits (median 27.5 vs. 31.3, $p < .11$) were seen in the lower targeted oxygen saturation group (13).

G. METHOD/ PROCEDURES

NICHD SUPPORT Trial Follow-on Study of Pulmonary Outcomes

G.1 Description of study design

This study will add an 18-22 month longitudinal, prospective follow-on study of surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial.

G.2 Definition of study population

Infants with gestational age of $24^{0/7}$-$27^{6/7}$ weeks' gestation by best obstetrical estimate.

Inclusion criteria:

- Full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Parents/legal guardians have provided consent for enrollment
- No known major congenital malformations
- Survival to hospital discharge

Exclusion Criteria

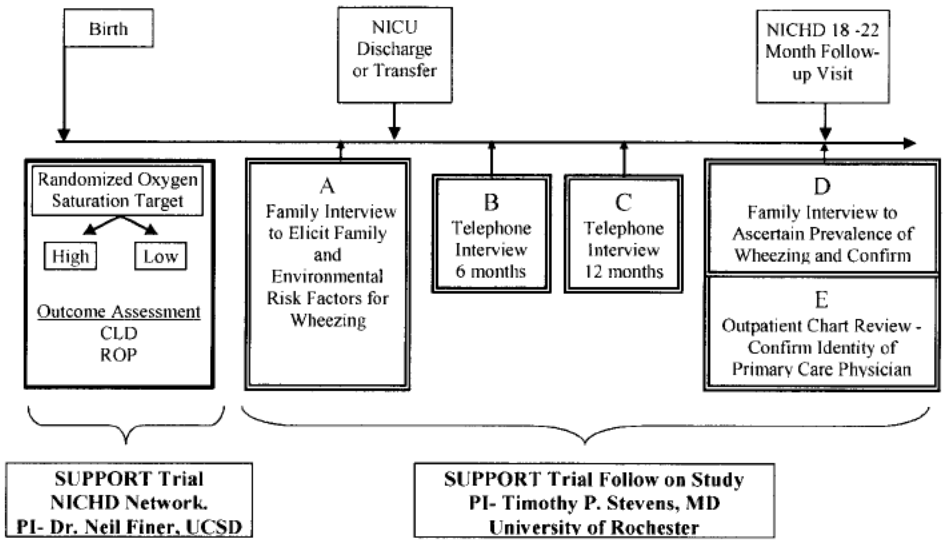
- Transport to the center after delivery
- Parents/legal guardians refuse consent
- Research apparatus/study personnel are not available.
- Gestational age $< 24^{0/7}$ or $\geq 28^{0/7}$ weeks' gestation

G.3 Description of study intervention

Before delivery, infants will be randomized to subsequent management with high vs. low target oxygen saturation according to the SUPPORT Protocol. The SUPPORT Follow-on Study proposed here begins just prior to NICU discharge (Figure 1).

SUPPORT Trial Follow-on Study

Figure 1. **Infants $24^{0/7}$-$27^{6/7}$ Weeks' Gestation**



"A" will be administered at NICHD Network Centers

"B-E" will be conducted long distance by University of Rochester research staff.

Fig 1, A. Parent (Guardian) Interview to Elicit Family and Environmental Risk Factors for Wheezing The family interview will be administered at each participating Network Center by site study nurses prior to NICU discharge or transfer. The questions are based on intake questions used by the Tucson Respiratory Study and are designed to elicit family history of asthma, atopy, and home environment and to identify likely care givers (Questionnaire in Appendix G). Consent for release of medical information will be obtained to facilitate contacting physician offices to obtain office data.

Fig 1, B. Telephone Interview at 6 months' CA – respiratory interval history

Fig 1, C. Telephone Interview at 12 months' CA – respiratory interval history

Telephone interviews will be undertaken at 6 and 12 months' to obtain limited interval history of respiratory problems including wheezing, medications used, and health services sought for respiratory related problems (Questionnaire in Appendix H).

Fig 1, D. Parental Interview to Ascertain Prevalence of Wheezing and Confirm Risk Factors This parent interview will also be administered by telephone, prior to the regularly scheduled 18-22 month NICHD developmental follow up clinic visit (an NICHD funded, ongoing program). Contacting parents prior to the office visit will help improve the Developmental Follow Up Clinic attendance rate and will allow the clinic visit to provide a back up means to contact the family. All telephone interviews, the 2 limited telephone interviews and the second family history interview at 18-22 months', will be conducted long distance from Rochester (see below). The interview questionnaires are based on questionnaires administered by the Tucson Respiratory Study at approximately one year of age (Questionnaire in Appendix I). Questions are designed to ascertain the frequency and severity of wheezing episodes. In addition, risk factors obtained at the 1st interview will be confirmed or updated.

Fig 1, E. Outpatient Chart Review - Confirm Identity of Primary Care Physician

To confirm results of physician report of wheezing obtained by telephone interview, patients undergoing telephone interview will have their primary care physician's medical record reviewed.

E.1 – Physician report of wheezing

E.2 – Frequency of outpatient pulmonary care. The volume of outpatient pulmonary care including outpatient primary care physician office visits, pulmonary specialty care, emergency room visits, hospitalizations and the number and duration of pulmonary medications will be obtained from primary care physician chart review. To help assure compliance by primary care office staff, a $25 honorarium will be offered for successful completion of the chart review form (45-47).

G.4 Precise definition of primary/secondary outcomes

1) Definition Of Parental Report Of Wheezing. The primary outcome will be parental report of recurrent wheezing, defined as more than 1 episode of wheezing, using questions adapted from the Tucson Children's Respiratory Study, questions validated in a large prospective birth cohort study of term infants (48-54) (Appendices G-I). The primary question used in the telephone interview for this project will be the same as the one used in the Tucson Children's Respiratory Study "Did your child have wheezing?" (48) Additional questions will be used to further characterize the wheezing episodes, identify wheezing associated with a viral illness (parental report of a "cold") and wheezing associated with environmental exposures. The prevalence of health services utilization (outpatient office visits for pulmonary care, ER visits, re-hospitalizations, bronchodilator therapy) for pulmonary reasons will also be collected during interviews. The Tucson study also ascertained frequency of office visits and use of respiratory medications. Of full term infants whose parents reported that their infant had an episode of wheezing, 40% had recurrent wheezing in the first 6 years compared with 22% of infants whose parents reported no episodes of wheezing in the first 3 years.

Parental Report of Wheezing Is A Reliable Outcome Measure of Airway Dysfunction

Evaluation of frequency and severity of respiratory symptoms and volume of pulmonary care has been used as the primary outcome in multiple follow up studies of term and premature infants (10;12;14;43). A recent review evaluated the value of respiratory symptom history ascertained by parental questionnaire in determining the risk for developing asthma in early childhood. By evaluating 9 large, longitudinal, full term birth cohort studies and reviewing the original questionnaire from 7 of these studies, Koopman found that the questions posed to parents

eliciting a history of wheezing in their infants were similar. Parental report of wheezing predicted an increased risk for later respiratory symptoms including asthma. In the studies proposed here, recurrent wheezing ascertained by parental report will be used as the primary outcome, rather than physiologic measurements of airway dysfunction, for several reasons (Table 3). Although the goal of using respiratory questionnaires in the studies proposed here is to measure pulmonary outcome, not to predict asthma, studies of asthma questionnaires and their ability to predict asthma demonstrates the validity of parental report of wheezing as an accurate measure of airway dysfunction.

Reasons to Use Parental Report of Wheezing as Primary Outcome Measure

- Parental interview can be performed more readily on large numbers of patients. The validity of this approach has been shown in several longitudinal studies including The Tucson Respiratory Study, upon which the interview questions are based.
- Recurrent wheezing is highly correlated with changes on pulmonary function testing. In a study of infants with CLD, a history of recurrent wheezing was associated with greater expiratory flow limitation, hyperinflation and airway responsiveness to albuterol on pulmonary function testing compared to those without a history of recurrent wheezing (24).
- Parental recall of respiratory illnesses has been shown to correlate strongly with review of medical office records. For asthma and bronchitis in the past year, Pless et al. found good agreement between recall of 288 parents and physician office chart review. Parental education and occupation were not predictive of a parent's ability to recall the illness (55). In an assessment of parental recall done to evaluate minor injury in children, Harel found recall declined with time, with the best recall occurring in the first 3 months' after injury with further decline after 6 months' from the time of the injury (47;56;57).

Advantages of Conducting Telephone Interviews From a Single Center

Conducting the telephone interviews from Rochester will:

1) require less effort from the individual Network Centers (Network Centers may assist in tracking families)
2) allow standardization of the telephone interview by a core group of trained interviewers
3) blind the telephone interviewer to the SUPPORT Trial study group designation
4) reduce the cost of the study by consolidating the telephone training and follow up at one site.

2) Definition Of Physician Diagnosed Wheezing. A secondary outcome will be physician report of recurrent wheezing, defined as more than 1 episode of wheezing. Physician diagnosed wheezing will be collected by parental report during telephone interviews using the question "Did a doctor tell you your child had wheezing?" and "Where did you see that Doctor, primary care, emergency room, hospital or other?" In addition, review of the primary care physician medical chart will be undertaken to identify episodes of physician documented wheezing.

3) Definitions of Secondary Outcomes - Measures of Volume of Outpatient Pulmonary Care

Important secondary outcomes of outpatient pulmonary morbidity will be collected (Table 1).

Table 1. ***Secondary Outcomes, Covariates and Sources***	
Outcomes	Source
Secondary Outcomes	
Number and duration of outpatient pulmonary medications including bronchodilator, diuretic, methylxanthine, and inhaled and systemic steroid therapy.	Family interview, primary care chart review
Number of office visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of emergency room visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of re-hospitalizations for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Growth at 18 months' CA (height, weight and head circumference)	NICHD follow up clinic data

Data Collection: Ascertainment of Outcomes - Field Work

Ascertainment of Wheezing and Outpatient Pulmonary Morbidity By Telephone Interview.
There will be 4 parental interviews over 18-22 months', one prior to NICU discharge and 3 subsequent telephone interviews at 6 month intervals to collect data on the prevalence of recurrent wheezing, need for outpatient pulmonary care, and relevant environmental and family history covariates (Figure 1, A-D above). Based on review of longitudinal studies of full term infants in which follow up patient contacts occurred quarterly to once every 18 months', a 6 month interval for follow up patient contacts is planned in an effort to reduce parental recall omissions which are more likely to occur with less frequent follow up (43;56). The 4 interviews are designed to collect the primary and secondary outcomes of the follow-on study. Other inpatient and outpatient data will be collected as part of the NICHD Neonatal Research Network Generic Database (GDB) and Follow-up Program.

The University of Rochester Neonatology Research Group has conducted similar telephone interview designs as part of an ophthalmologic outcome study of patients enrolled in a randomized trial of cryotherapy to treat ROP and a 15-year, longitudinal neurological assessment conducted by telephone survey among 132 infants treated with surfactant. Telephone follow up rates were 96% follow up at 7 years and 95% follow up at 15 years (58). In the study proposed here, the University of Rochester Health Services Research Group (HSR Group), will conduct the telephone interviews.

In telephone follow up surveys conducted by the HSR Group, follow up rates at 12 months' have exceed 75% in populations at high risk for being lost to follow up (59-65). The Rochester HSR Group has over 2,500 square feet of newly renovated space. Under the direction of Drs. Jonathan Klein and Peter Szilagyi, the HSR group includes sufficient space and all appropriate equipment and personnel to perform telephone interviews and database management for the project presented here. The HSR Group will conduct 3 telephone interviews from Rochester. Drs. Peter Szilagyi and Jonathan Klein, co-directors of the HSR Group, are mentors for Dr. Stevens' K23 Patient Oriented Research Award application. Drs. Klein and Szilagyi will work with Dr. Stevens and Dr. Phelps in the implementation and management of the tracking and respiratory questionnaire program. To facilitate tracking and record keeping, Dr. Stevens will design and write a database to track enrolled patients and their contact information, next scheduled interview, and record answers to phone interview questions. Each interview will close with a question as to whether the family plans a new address or phone number prior to the next interview. The names and phone number of a friend or relative and their primary care physician will be sought so that they may be contacted in the event that contact with the patient is lost. By interviewing families every 6 months', a higher follow up rate will be achieved because family contact information will not become so out of date that the family is lost or that re-contacting them is inefficient. We anticipate that each interview will require 2 hours of staff time, with 20-30 minutes to conduct the interview and 90 minutes to contact family and enter data.

Interview Instruments – (Appendices A-C) Questionnaires based on the Tucson Children's Respiratory Study, a well validated questionnaire used in a large longitudinal cohort study that followed healthy full term infants from birth to over 20 years of age. The questionnaires have been updated to reflect currently available respiratory medications and modified to address the health issues that are faced by formerly premature infants such as use of palivizumab for RSV prophylaxis. In addition, the questionnaires are designed to elicit a thorough history of possible covariates, such as environmental and infectious exposures and family histories of atopy, asthma or respiratory disease.

Physician Office Records Assessment of Wheezing and Outpatient Pulmonary Morbidity Physician office charts will be reviewed to determine physical findings of wheezing, medication use and respiratory related hospitalization history. For primary care pediatricians, the family's consent authorizing release of medical information and an office contact questionnaire will be mailed or faxed to the provider. The questionnaire will be based on a similar document used by the Rochester Research Group to obtain medical information on respiratory issues. To help assure compliance with completing the questionnaire, a $25 honorarium will be offered to the office staff.

Data Collection: Ascertainment of Environmental and Genetic Covariates

Ascertainment of important environmental exposures and genetic risk factors that might confound the relationship between supplemental oxygen exposure and recurrent wheezing will be obtained along with the primary outcome during the same telephone and family interviews (Table 2). A second follow-on study to the SUPPORT Trial, not affiliated with the studies proposed here, is being independently proposed by other investigators to study specific genetic markers that predict greater risk of CLD. Although synergy between our study and the genetic study potentially exists, the genetic study is not yet funded and may not go forward.

Table 2. Postnatal and Genetic Covariates Evaluated as Potential Confounders of Oxygen and Wheezing

Covariates in Home Environment and Exposures The initial questionnaire and 6 month interviews will gather information on other *inhaled exposures* (tobacco, wood stoves, cold air), *residence* (urban vs. rural residence), *infectious exposures* (RSV, palivizumab) and medical risk factors (gastroesophageal reflux, congenital anatomic airway abnormalities)

Covariates in Family History Questionnaires will elicit *family history* of atopy (family history of asthma, eczema or allergy to foods, pets, molds, pollen or dust).

Data Collection: Ascertainment of Primary Exposure

Oxygen Exposure. In the SUPPORT Trial, it is assumed that managing infants with higher vs. lower targeted oxygen saturation range will result in different levels of supplemental oxygen exposure. Because oxygen is the primary exposure in the SUPPORT Follow-on Study and plays a central role in the disease model proposed, oxygen exposure will be quantified carefully. To document the difference in oxygen exposure between groups, FIO2 values will be recorded and analyzed as described in the SUPPORT Trial.

G.5 Sample size estimate with some statistical support based upon primary outcome

The SUPPORT Trial anticipates enrollment of 1506 patients < 28 weeks' gestation, providing 80% power to detect a 10% difference between treatment groups in the incidence of death/CLD and death/stage III Retinopathy of Prematurity (ROP). Assuming mortality of 35% for infants < 1000 grams (NICHD 2002 data), 978 infants would be expected to survive and be eligible for the SUPPORT follow-on study.

Power for detecting a difference between the high vs. low saturation groups for the primary outcome, recurrent wheezing We expect the prevalence of wheezing to be about 0.17 in the low saturation group, and about 0.31 in the high saturation group(12). For the power calculations, we also consider a scenario with a smaller difference between groups: 0.19 for the low saturation group and 0.29 for the high saturation group. We expect the follow up rate to be about 75%, which would result in data on about 733 patients. We also consider a lower follow up rate of 65%, which would result in about 635 patients. Power to detect a difference between groups based on a chi-square test with type I error alpha set at 0.05 is given in Table 7 for each scenario. From those results, we expect to have more than 80% power for the primary outcome. Also of interest are subgroup analyses, where we look separately at the CLD and non-CLD subjects. Of survivors, we expect 37% or 362 infants to have CLD. For the CLD group, we expect the prevalence of wheezing to be about 0.5 in the high saturation group and 0.3 in the low saturation group. If there is a 75% follow up rate, we will have 92% power to detect a difference between the two groups. For the non-CLD subgroup, we expect the prevalence to be 0.2 and 0.1 in the high and low groups, respectively. With 75% follow up, we will have 85% power. Thus, we expect to have adequate power for the primary outcome even in the analyses stratified by CLD.

Table 3. Power for primary outcome, recurrent wheezing.

Follow up rate	Low Saturation	High Saturation	power
75%	0.17	0.31	0.99
75%	0.19	0.29	0.88
65%	0.17	0.31	0.98
65%	0.19	0.29	0.84

We expect the study to be adequately powered for analysis of important secondary outcomes such as use of pulmonary medications. Based on results reported in Davis et al. for infants less than 27 weeks' gestational age [22], we expect the prevalence rate of pulmonary medications to be 0.42 in the high saturation group, and 0.19 in the lower saturation group. In that case, even with a 65% follow up rate, we would have more than 99% power to detect a difference between the groups with a chi-square test. Similarly, the CLD subgroup analyses would have more than 80% power under those assumptions. Based on the power numbers above, we could potentially enroll fewer subjects in the trial and still have adequate power. However, we choose to over enroll slightly to make up for the fact that some patients will likely be lost to follow up.

Data Analysis.

Analysis of primary dichotomous outcomes will be performed by chi square test and presented as a relative risk for development of that outcome. Number of outpatient pulmonary visits for respiratory illnesses will be presented as median values. The Wilcoxon Rank Sum test, a non-parametric alternative to the two-sample t-test, will be used to test for differences between the two groups. Statistical analyses will need to consider the effect of multiple comparison groups on the level of statistical significance. All analyses will be performed in conjunction with the Research Triangle Institute (RTI, North Carolina), the biostatistical support group for the NICHD Neonatal Network. Data will be presented as shown in tables 4-5. Mean FIO2 values in the high and low SpO2 groups will be compared by two sample t-test. Secondary analyses will be done to evaluate the effect of ventilator strategy on pulmonary outcome and presented similarly to table 4 and 5.

Table 4. ***Primary Dichotomous Outcomes***	**Low Saturation**	**High Saturation**	**RR**	**CI**	**p-value**
Parental Report of Recurrent Wheezing (%)					
Physician Diagnosed Recurrent Wheezing (%)					
Need for Outpatient Pulmonary Medications (%)					
Need for Physician Visit for Respiratory Illness (%)					
Need for Re-hospitalization for Respiratory Illness (%)					

Table 5. ***Primary Outcomes – Continuous Outcomes***	**Low Saturation**	**High Saturation**	**p-value**
Number of Physician Visit for Respiratory Illness (Median)			
Number of Emergency Visits for Respiratory Illness (Median)			
Number of Re-hospitalization for Respiratory Illness (Median)			

Expected Results We predict that premature infants managed with a lower targeted oxygen saturation range compared to those managed with a higher targeted oxygen saturation are exposed to lower levels of supplemental oxygen and have reduced risk of recurrent wheezing in the first 18-22 months' CA.

Anticipated Problems and Solutions

1) Participant attrition. As seen in the sample size calculation, the potential for patients to be lost to follow up over time will be offset by over enrolling patients to participate in the follow up. Because patients who enroll in the SUPPORT Trial are randomized, there should be no systematic bias favoring one group over another among patients who are lost to follow up. However, if loss to follow up is in part caused by the treatment or outcomes, this could bias the results. We will therefore investigate whether there are differences in key variables for subjects who are lost to follow up compared to those who remain in the study. For example, we will test whether subjects in one treatment arm were more likely to be lost to follow up than in the other arm. Similarly, we will compare wheezing rates at 6 months' for those who are later lost to follow up compared to those who remain in the study. We do not expect to see any major differences.
2) Low office respiratory health questionnaire response rate. For primary care offices that do not respond to the first mailing, a repeat questionnaire will be mailed. A phone call to the office will be made if there is no response to the second mailing. A $25 honorarium will also be offered to encourage replies.

3) The SUPPORT Follow-on Study of Pulmonary Outcomes has been prepared as the central project for Dr. Stevens' Patient Oriented Clinical Research Grant (K23 Award), submitted 10/1/04. If approved, funds from the K23 will be available to offset a portion of the cost of conducting this SUPPORT Trial Follow-on study. In the event that the K23 is not funded, I will seek additional funding from alternative sources including The American Lung Association and The March of Dimes Foundation.

G.6 Available population/compatibility with other ongoing protocols

Another secondary study proposed by a group independent from ours is looking at the genetics of reactive airways disease in patients enrolled in the SUPPORT Trial. The follow on study proposed here should be complementary to the genetics study, enhancing the both the quality and quantity of data on the prevalence of wheezing and need for outpatient pulmonary care in patients enrolled in the SUPPORT Trial.

G.7 Estimate of projected recruitment time

The recruitment time will be that of the SUPPORT Trial with a 18-22 month period of follow up to ascertain primary and secondary outcomes.

H. RISKS/BENEFITS, WITH ESTIMATE OF FREQUENCY/SEVERITY OF RISKS.

By using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care may be quantified, allowing assessment of whether infants who develop CLD and those who do not have improved pulmonary health as a result of the study intervention. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the follow up visit. We anticipate no risk to the patient of this observational follow on study.

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SUPPORT FOLLOW-ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED AT TIME OF ENROLLMENT
PRIOR TO NICU DISCHARGE

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

Appendix A

QUESTIONNAIRE: ENROLLED CHILD
(Nurse Administered)

Child's Name: _____ Date: ____/____/____
Mo. Day Yr.

Child's Sex 1. Male 2. Female

Child's Birthdate ____/____/____ Apgar ____/____
Mo. Day Yr.

Person being interviewed:

1. Child's Mother
2. Child's Father
3. Both Parents
4. Child's female guardian
5. Child's male guardian
6. Other woman (SPECIFY RELATIONSHIP) _____
7. Other man (SPECIFY RELATIONSHIP) _____

1. At this time, we would like a little information about the environment in which your new child will grow up. First, how many people live with you in your home?

Total household members: _____

2a. After the first few months, will your child be sharing a room with other family members on a regular basis?

1. Yes
2. No

2b. IF YES: How many people will sleep in the same room with him/her? _____

2c. How many living areas are there in your house, excluding closets and bathrooms?_____

3. How many pets are there in the household, either kept inside or out? (RECORD THE NUMBER OF EACH LIVING IN AND OUT OF THE HOUSE).

	Number Kept Inside	Number Kept Outside
Dogs	_____	_____

Cats	_____		_____
Gerbils, Hamsters and Guinea Pigs	_____		_____
Other (Please specify type)			
_____	_____		_____
_____	_____		_____

4. On a scale of 1 to 5, where 1 is not dusty and 5 is very dusty, how dusty would you say your home is compared to other homes in your neighborhood? (CIRCLE APPROPRIATE NUMBER).

Not at all Dusty — Very Dusty

5. Does your home or apartment have air conditioning or some kind of cooling?
   1. Air Conditioning
   2. Evaporative Cooling
   3. Both
   4. None
   5. Other _____
   6. Don't Know

6. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).
   1. Steam or hot water (radiator)
   2. Central gas furnace (furnace)
   3. Electric
   4. Wood Stove
   5. Other
   6. Don't know

7. What fuel is used most for cooking in your home?
   1. Electricity
   2. Gas
   3. Fuel Oil
   4. Wood Stove
   5. Other
   6. Don't Know

8a. Is your child being breast fed? 1. Yes 2. No...SKIP TO QUESTION 9

IF YES,

b. Will this be supplemented with formula? 1. Yes 2. No

c. When do you think the supplement will begin? _____months

d. Do not know when supplements will begin. 1. Yes 2. No

9. Does the mother plan to work outside the home within the next year?
   1. Yes
   2. No
   3. Don't Know

10a. Will your child be cared for by anyone who is not an immediate family member for a major part of the next year?
   1. Yes
   2. No
   3. Maybe

IF YES or MAYBE to 10a:

b. Where will this care be provided?
   1. The parent or guardian's home?
   2. Home of a relative or private sitter?
   3. Day care setting (non-private) ?
   4. Don't Know

c. Will this involve other children, not counting the child's brothers and sisters?
   1. Yes
   2. No

12. Finally, which relative is most likely to have your address in case we lose contact with you?

_____ _____
Name Relationship

_____
Address

_____

SUPPORT FOLLOW ON STUDY
FAMILY HISTORY / FAMILY CONTACT QUESTIONNAIRE - ADMINISTERED PRIOR TO NICU DISCHARGE

1. Name:				
2. Relationship to enrolled child:	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact
3. Age (in years):	__________	__________	__________	__________
4. Sex:	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female
5. Does this person currently have:	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
a. Bronchitis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
b. Emphysema?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
c. Bronchiectasis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
d. Asthma?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
e. Inhaled Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
f. Food Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
g. Any other chronic respiratory disease? (SPECIFY)	__________ __________	__________ __________	__________ __________	__________ __________
6. How often does this person smoke in the house?	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently

SUPPORT FOLLOW ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED BY TELEPHONE AT 6 AND 12 MONTHS CORRECTED AGE

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Before we begin this interview it would be helpful if you could gather any medications your child has been prescribed or has been taking and have them in front of you. Can you do that now or is there a better time to call you?

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing concerns your child may have.

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

4a. Has his/her chest ever sounded wheezy or whistling?
   3. Yes
   4. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?

1	2	3	4	5
Very rarely				On Most days

e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing ~

g. Has this child's wheezing/whistling occurred as attacks?
   1. Yes
   2. No

h. Has this child ever been awakened at night by wheeze or by shortness of breath?
   1. Yes
   2. No

i. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

j. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES. BE SURE TO COMPLETE QUESTIONS 24 AND 25

5. Does this child's chest sound wheezy or whistling during or shortly after vigorous exercise or crying?
   1. Yes, usually
   2. Yes, occasionally
   3. No

6a. Has he/she ever had episodes of shortness of breath or chest tightness?
   1. Yes
   2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6A:

b. Has this ever occurred when the child is at rest?
   1. Yes
   2. No

c. During the past year, how many episodes did he/she have?

1 2 3 4 5
Few Very many

d. How old was this child when he/she had the first such episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

OR: check here if the child still has condition: ~

f. Has the child's chest ever sounded wheezy or whistling during episodes of shortness of breath or chest tightness?
   1. Yes
   2. No

g. Has he/she ever seen a doctor for shortness of breath or chest tightness?
   1. Yes
   2. No

h. Has this child ever taken any medicine for shortness of breath?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

7. Has this child ever had a cough when he/she did not have a cold?
   1. Yes
   2. No . . . SKIP TO QUESTION 6

IF **YES** TO QUESTION 5a

b. At what time of the day has this cough usually occurred? (CIRCLE ALL THAT APPLY)
   1.
   1. In the morning, shortly after rising
   2. Later in the day
   3. During the night
   4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?
   1. Yes
   2. No

d. How often has this child been bothered by coughing?

1	2	3	4	5
Very Rarely				On most days

e. How old was the child when he/she first began to cough?
   ____ months

   OR: check here if child is still coughing: _

f. How old was this child when he/she stopped coughing?
   _____ months

g. Has the cough usually been dry or loose?
   1. Dry
   2. Loose

h. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?
   1. Yes
   2. No

i. How often has your child raised phlegm, sputum or mucus when coughing?
   1. Never
   2. Occasionally
   3. Often

j. Has he/she ever seen a doctor about the cough?
   1. Yes
   2. No

Does this child cough during or shortly after vigorous exercise?
   1. Yes, usually
   2. Yes, occasionally
   3. No

8a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 9a

IF **YES** TO QUESTION 8A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: ~

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ months

OR: check here if doctor never said he/she had asthma: ~

e. **During the past year**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past year**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

9a. Has your child ever had bronchitis?

1. Yes
2. No . . . SKIP TO QUESTION 10a

IF **YES** TO QUESTION 9a:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last episode occurred?

_____ months

OR: check here if child still has bronchitis ___

d. How old was this child when you were first told by a doctor that he/she had bronchitis?

_____ months

OR: check here if doctor never said he/she had bronchitis___

e. How often has this child had bronchitis?

1. one episode only
2. 2-3 episodes
3. 4 or more separate episodes
4. almost constantly

f. During the past year, how much trouble did he/she have with bronchitis?

1 2 3 4 5

None A great deal

g. During the past year, did this child take any medicine for bronchitis?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 254

10a. Has your child ever had croup?

1. Yes
2. No . . . SKIP TO QUESTION 11a

IF **YES** TO QUESTION 10a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of croup?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

11a. Has your child ever had bronchiolitis, or any wheezing illness in the first year of life not due to asthma?

1. Yes
2. No . . . SKIP TO QUESTION 12a

IF **YES** TO QUESTION 11A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

12a. Has your child **ever** had pneumonia?

1. Yes
2. No . . . SKIP TO QUESTION 13

IF **YES** TO QUESTION 12a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

13a. Was this child breast fed?

1. Yes
2. No . . . SKIP TO QUESTION 14

IF **YES** TO QUESTION 13a:

b. For how many months was this child breast fed?

1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

14a. Has the mother smoked at all since this child was born?

1. Yes
2. No . . . SKIP TO QUESTION 15a

IF **YES** TO QUESTION 14a:

b. For how many months did the mother smoke since this child was born?

_____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES)

_____ cigarettes
_____ pipes
_____cigars
_____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?

Never
Occasionally
Frequently

15a. Has the father smoked at all since the child was born?

1. Yes
2. No . . . SKIP TO QUESTION 16

IF **YES** TO QUESTION 15a:

b. For how many months did the father smoke since this child's birth?

_____ months

c. On the average, how many of each of the following did he smoke per day during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES).

_____ cigarettes
_____ pipes
_____ cigars
_____ non-tobacco cigarettes

d. How often has the father smoked in the same room with this child?

1. Never
2. Occasionally
3. Frequently

16. Did any other household member regularly smoke in the house since this child's birth?

1. Yes
2. No

17. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

18. How many brothers and sisters (including half siblings) does this child have?

_____

19a. Are there any other children living in your household **besides** this child and all of his/her siblings?

1. Yes
2. No . . . SKIP TO QUESTION 20

IF **YES** TO QUESTION 19a:

b. How many children other than this child and his/her siblings live in your house?

_____

20. Do you have any pets?

1. Yes
2. No

1❑ Dogs #: _____
2❑ Cats #: _____
3❑ Other #: _____

21. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).

1. steam or hot water
2. central gas furnace
3. wall or floor gas furnace
4. electric
5. other
6. don't know

OUTPATIENT RESPIRATORY PROPHYLAXIS

22. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?

1. Yes
2. No

23. Did this child receive a flu shot?

1. Yes
2. No

OUTPATIENT RESPIRATORY SUPPORT

24a. Is your child on any oxygen therapy (oxygen tank at home)?

1. Yes
2. No

IF **YES** TO QUESTION 24a:

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

*lpm = liters per minute

25. Is your child taking any medicines for asthma or wheezing?

1. Yes
2. No
3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as*: ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other _____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

THANK YOU FOR YOUR COOPERATION

SUPPORT FOLLOW ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED AT 18-22 MONTH FOLLOW UP VISIT

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing concerns your child may have.

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

4a. Has his/her chest ever sounded wheezy or whistling?
   1. Yes
   2. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?

1	2	3	4	5
Very rarely				On Most days

e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing _

g. Has this child's wheezing/whistling occurred as attacks?
   1. Yes
   2. No

h. Has this child ever been awakened at night by wheeze or by shortness of breath?
   1. Yes
   2. No

i. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

j. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

5. Does this child's chest sound wheezy or whistling during or shortly after vigorous exercise or crying?
   1. Yes, usually
   2. Yes, occasionally
   3. No

6a. Has he/she ever had episodes of shortness of breath or chest tightness?
   1. Yes
   2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6A:

b. Has this ever occurred when the child is at rest?
   1. Yes
   2. No

c. During the past year, how many episodes did he/she have?

1 2 3 4 5
Few Very many

d. How old was this child when he/she had the first such episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

OR: check here if the child still has condition: _

f. Has the child's chest ever sounded wheezy or whistling during episodes of shortness of breath or chest tightness?
   1. Yes
   2. No

g. Has he/she ever seen a doctor for shortness of breath or chest tightness?
   1. Yes
   2. No

h. Has this child ever taken any medicine for shortness of breath?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

7. Has this child ever had a cough when he/she did not have a cold?
   1. Yes
   2. No . . . SKIP TO QUESTION 6

IF **YES** TO QUESTION 5a

b. At what time of the day has this cough usually occurred? (CIRCLE ALL THAT APPLY)
   1.
   1. In the morning, shortly after rising
   2. Later in the day
   3. During the night
   4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?
   1. Yes
   2. No

d. How often has this child been bothered by coughing?

1	2	3	4	5
Very Rarely				On most days

e. How old was the child when he/she first began to cough?
   ____ months

   OR: check here if child is still coughing: _

f. How old was this child when he/she stopped coughing?
   _____ months

g. Has the cough usually been dry or loose?
   1. Dry
   2. Loose

h. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?
   1. Yes
   2. No

i. How often has your child raised phlegm, sputum or mucus when coughing?
   1. Never
   2. Occasionally
   3. Often

j. Has he/she ever seen a doctor about the cough?
   1. Yes
   2. No

Does this child cough during or shortly after vigorous exercise?
   1. Yes, usually
   2. Yes, occasionally
   3. No

8a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 9a

IF **YES** TO QUESTION 8A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: _

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ _ months

OR: check here if doctor never said he/she had asthma: _

e. **During the past year**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past year**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

9a. Has your child ever had bronchitis?

1. Yes
2. No . . . SKIP TO QUESTION 10a

IF **YES** TO QUESTION 9a:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last episode occurred?

_____ months

OR: check here if child still has bronchitis ___

d. How old was this child when you were first told by a doctor that he/she had bronchitis?

_____ months

OR: check here if doctor never said he/she had bronchitis___

e. How often has this child had bronchitis?

1. one episode only
2. 2-3 episodes
3. 4 or more separate episodes
4. almost constantly

f. During the past year, how much trouble did he/she have with bronchitis?

1 2 3 4 5

None A great deal

g. During the past year, did this child take any medicine for bronchitis?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 254

10a. Has your child ever had croup?

1. Yes
2. No . . . SKIP TO QUESTION 11a

IF **YES** TO QUESTION 10a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of croup?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

11a. Has your child ever had bronchiolitis, or any wheezing illness in the first year of life not due to asthma?

1. Yes
2. No . . . SKIP TO QUESTION 12a

IF **YES** TO QUESTION 11A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

12a. Has your child **ever** had pneumonia?

1. Yes
2. No . . . SKIP TO QUESTION 13

IF **YES** TO QUESTION 12a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

13a. Was this child breast fed?

1. Yes
2. No . . . SKIP TO QUESTION 14

IF **YES** TO QUESTION 13a:

b. For how many months was this child breast fed?

1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

14a. Has the mother smoked at all since this child was born?

1. Yes
2. No . . . SKIP TO QUESTION 15a

IF **YES** TO QUESTION 14a:

b. For how many months did the mother smoke since this child was born?

_____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES)

_____ cigarettes
_____ pipes
_____cigars
_____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?

Never
Occasionally
Frequently

15a. Has the father smoked at all since the child was born?

1. Yes
2. No . . . SKIP TO QUESTION 16

IF **YES** TO QUESTION 15a:

b. For how many months did the father smoke since this child's birth?

_____ months

c. On the average, how many of each of the following did he smoke per day during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES).

_____ cigarettes
_____ pipes
_____ cigars
_____ non-tobacco cigarettes

d. How often has the father smoked in the same room with this child?

1. Never
2. Occasionally
3. Frequently

16. Did any other household member regularly smoke in the house since this child's birth?

1. Yes
2. No

17. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

18. How many brothers and sisters (including half siblings) does this child have?

_____

19a. Are there any other children living in your household **besides** this child and all of his/her siblings?

1. Yes
2. No . . . SKIP TO QUESTION 20

IF **YES** TO QUESTION 19a:

b. How many children other than this child and his/her siblings live in your house?

_____

20. Do you have any pets?

1. Yes
2. No

1❑ Dogs #:_____
2❑ Cats #: _____
3❑ Other #:_____

21. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).

1. steam or hot water
2. central gas furnace
3. wall or floor gas furnace
4. electric
5. other
6. don't know

OUTPATIENT RESPIRATORY PROPHYLAXIS

22. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?

1. Yes
2. No

23. Did this child receive a flu shot?

1. Yes
2. No

OUTPATIENT RESPIRATORY SUPPORT

24a. Was your child ever on any oxygen therapy (oxygen tank at home)?

1. Yes
2. No

IF **YES** TO QUESTION 24a:

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

*lpm = liters per minute

25. Is your child taking any medicines for asthma or wheezing?

1. Yes
2. No
3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as*: ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other _____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

ATOPY HISTORY

26. **During the past year**, for how many days has this child been unable to do his/her usual activities because of illnesses such as chest (not head) colds, bronchitis, asthma or pneumonia?

_____ days

27. How many head colds (common colds) **per year** does this child usually have?

1. Few (0-3 per year)
2. Some (4-5 per year)
3. Frequent (6-9 per year)
4. Constant (more than 9 per year)

28a. Has your child **ever** had hay fever or any other condition that makes his/her nose runny, stuffy, or itchy **apart** from colds?

1. Yes
2. No . . . SKIP TO QUESTION 29

IF **YES** TO QUESTION 28a:

b. How old was your child when you first noticed this condition?

_____ months

c. How old was this child when he/she stopped having this condition?

_____ months

OR: check here if child still has condition ~

d. When this child has the runny or stuffy nose, does he/she also usually:

Cough?	1. Yes 2. No
Wheeze?	1. Yes 2. No
Have shortness of breath?	1. Yes 2. No

29. Has this child **ever** had allergies which cause nose, eye or lung problems?

1. Yes
2. No

30. Has a doctor **ever** told you that this child had sinus trouble?

1. Yes
2. No

31a. Has this child **ever** been allergic to any food?

1. Yes
2. No

b. Has he/she **ever** been allergic to any medicine?

1. Yes
2. No

32a. Has this child **ever** had eczema (allergic skin rash)?

1. Yes

2. No . . . SKIP TO QUESTION 33a

IF **YES** TO QUESTION 32A:

b. Has a doctor told you this child had eczema?
   1. Yes
   2. No

c. At what age did the eczema begin?
   _____ months

d. How old was this child when he/she last had eczema?
   _____ months

   OR: check here if child still has eczema ~

33a. Was this child breast fed?
   1. Yes
   2. No . . . SKIP TO QUESTION 34

IF **YES** TO QUESTION 33a:

b. For how many months was this child breast fed?
   1. Less than 1 month
   2. 1-3 months
   3. 4-6 months
   4. more than 6 months

34. At what age was formula introduced?
   1. Never
   2. less than 1 month
   3. 1-3 months
   4. 4-6 months
   5. more than 6 months

35. At what age was cow's milk (nonformula) started?
   1. Never
   2. Less than 1 month
   3. 1-3 months
   4. 4-6 months
   5. 7-9 months
   6. 9-11 months
   7. 12 or more months

36. At what age did he/she begin to receive table foods?
   1. less than 1 month
   2. 1-3 months
   3. 4-6 months
   4. 7-9 months
   5. more than 9 months

THANK YOU FOR YOUR COOPERATION

Protocol for the NICHD Neonatal Research Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial

Final

August 28, 2004
Revised September 16, 2004

1.1 Statement of Problem

At the present time, there is no recommendation or standard teaching regarding the early use of CPAP/PEEP during resuscitation and continuing after NICU admission for the extremely low birth weight (ELBW) infant. However, a number of studies, mostly retrospective in nature, have suggested that the use of early CPAP may be associated with improved outcomes, including a decreased need for mechanical ventilation, a decreased need for surfactant therapy, and a decrease in oxygen supplementation and/or death at 28 days after birth and at 36 weeks post menstrual age. There has not been a prospective study which has randomized ELBW infants to CPAP/PEEP beginning in the delivery room, and continuing in the NICU and a permissive ventilation strategy if intubation is required and compared their outcomes to infants treated with prophylactic or early natural surfactant, interventions with known efficacy in reducing mortality, severity of disease and the incidence of chronic lung disease (CLD).

Retinopathy of prematurity (ROP) remains a significant cause of morbidity among ELBW infants and its occurrence is inversely proportional to gestational age and duration of oxygen exposure. It is known that ROP is increased by the prolonged use of supplemental oxygen from observations published in the 1950s, and but early trials were unable to pinpoint the actual level of arterial PaO_2 which was the threshold for triggering the pathophysiology of this disorder.[1] However, there have been a very few prospective studies evaluating the benefit of higher versus lower levels of oxygenation in infants, especially for ELBW infants, none of which were performed during the acute illness. While retrospective cohort studies have suggested that the use of lower SpO2 ranges and adherence to strict nursery policies may result in a lower incidence of severe ROP, there is no current agreement on the accepted SpO2 ranges for managing the ELBW infant from birth.

1.2 Background

Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC). Although no formal recommendation has been made to date about maintaining PEEP in the delivery room setting, continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[2]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9hours ($\pm$12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[3] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[4]. Premature infants who do not achieve a FRC are more likely to develop hyaline membrane disease (HMD) requiring mechanical ventilation[5]. CPAP may prevent the excessive consumption of surfactant in newborn infants with limited surfactant production.[6] A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era suggested that early CPAP may improve survival in infants greater than 1500 gm.[7]

Similarly, there is no definite recommendation or standard teaching regarding the level of oxygenation that should be maintained in ELBW infants. Oxygen supplementation has to be used liberally as ELBW infants frequently have desaturation episodes and thus wide saturation ranges are tolerated clinically. However, oxygen toxicity can result in increased risk for CLD, retinopathy of prematurity (ROP) and other disorders. Alternatively, oxygen restriction may impair neurodevelopment. The pulse oximeter is a newer technology that can be used to improve the control of oxygenation levels. There is great potential benefit to determining the oxygenation levels that prevents ROP and CLD but does not result in neurodevelopmental impairment with a randomized controlled trial of levels of oxygen saturations on the high and low side of the currently utilized levels.

While prevention of hyperoxia may decrease the risk for ROP and CLD, efforts to maintain lower oxygenation levels may result in an increase in periods of hypoxemia because of the marked variability in oxygen in ELBW infants. Thus, it is necessary to determine if lower oxygenation levels that may prevent ROP and CLD are deleterious for brain development and result in impaired neurologic outcome.

1.3 Animal Studies

Nilsson et al demonstrated that the use of 5 cm H_2O PEEP in the initial ventilation of premature rabbit pups resulted in increased lung-thorax compliance, and reduced the extent of bronchiolar epithelial lesions seen with mechanical ventilation [8]. The use of early PEEP starting at delivery, improves the response to surfactant, improves lung mechanics increases surfactant pools, and reduces lung injury. [9,10]

More recently studies by Jobe et al have demonstrated that premature lambs treated with CPAP alone at birth had significantly decreased neutrophils and hydrogen peroxide in their alveolar wash when compared with animals who were ventilated from birth. [11]

1.4 Human Experience: Ventilatory Support

CPAP was introduced by Gregory et al in 1970 and was shown to improve gas exchange and outcomes in preterm infants with respiratory distress.[12] A subsequent review of CPAP for respiratory distress concluded that "In preterm infants with RDS the application of CDP either as CPAP or CNP is associated with benefits in terms of reduced respiratory failure and reduced mortality. CDP is associated with an increased rate of pneumothorax. The applicability of these results to current practice is difficult to assess, given the intensive care setting of the 1970s when four out of five of these trials were done." [13]

There is now a body of information from Europe that provides further evidence that early CPAP can reduce the need for intubation in a significant number of VLBW infants. Jonsson et al treated VLBW infants from 1988 to 1993 that required > 30% oxygen with nasal CPAP usually within 30 minutes of delivery[14]. From 1991 onward, infants with severe distress or apnea were intubated for a $PaCO_2$ greater than 60 mmHg, and were given surfactant. Twenty-five percent of all infants required only supplemental oxygen and 24% of all infants were ventilated from birth. Fifty-one percent were treated with nasal CPAP, with one-third of these subsequently requiring ventilation. Almost all infants < 24 weeks required ventilation suggesting that this group may require a different approach. Gittermann et al reported that the use of early CPAP for infants < 1500gm (VLBW) significantly reduced the frequency of intubation, reduced mortality ($p=0.038$), and shortened the duration of intubation and length of stay[15]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[16] in a report of 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 reported that there was an increase in the proportion of patients not intubated and mechanically ventilated from 7% to 14% in infants <1000 g and from 28% to 44% in those $\geq$1000 g ($P < 0.02$ and <0.01, respectively). The decrease in intubation was not associated with a significant increase in adverse outcome such as death, intraventricular hemorrhage, periventricular leukomalacia, or BPD. The proportion of infants <1000 g that survived without BPD increased from 38% in 1992 to 48% in 1994; $p < .05$, and the proportion of infants =1000 g in whom BPD developed decreased from 14% to 9%; $p < .05$. None of these observations was from a prospective controlled trial, and in none was there a contemporaneous control group who did not receive early CPAP.

The first prospective trial comparing prophylactic CPAP, started at birth, with conventional management was that of Han et al. They compared the use of nasal CPAP given by nasopharyngeal tube with conventional management in 82 infants, 32 weeks gestational age at birth, and in this study it would appear that CPAP was begun in the DR, but may have been delayed for up to 2 hours.[17] No infants in this trial received surfactant, and no mothers were treated with antenatal steroid. There was no advantage observed with the use of early CPAP, and oxygenation was worse in the early CPAP treated infants. The reviewers of the use of prophylactic CPAP in the Cochrane library concluded that "A multicenter randomized controlled trial comparing prophylactic nasal CPAP with "standard" methods of treatment is needed to clarify its clinical role."[18]

In the post surfactant era, Verder et al conducted the first prospective evaluation of early CPAP (not necessarily delivery room CPAP) and short-term intubation for surfactant administration in a multicenter collaborative trial conducted from September 1991 to October 1992.[19] The primary hypothesis was that the use of early CPAP and brief intubation for surfactant in infants meeting pre-established criteria would reduce the percentage of infants requiring mechanical ventilation from 80% to 40%. Infants randomized to surfactant [Curosurf®] received 200 mg/kg, (2.5 ml/kg) following intubation, with manual ventilation for 2-5 minutes and were then extubated if stable. This study was stopped after an interim analysis demonstrated a significant benefit for the surfactant treated infants. Thirty-three of the 35 infants randomized to early surfactant were extubated after such treatment, and 13 required reintubation at a median of nine hours after surfactant treatment, compared with 28 of 33 control infants who were intubated a median of three hours after randomization, (p=0.003). The overall duration of ventilation in both groups was 2.5 days; there were no other differences between the groups. Verder et al performed a second multicenter prospective trial from April 1995 to January 1997 and enrolled infants <30 weeks with similar criteria to the previous trial, apart from an entry a/A ratio of .35 to .22, which decreased over 30 minutes, which was less stringent, allowing infants to be treated at lesser degrees of oxygen requirement, than their first study. These infants were initially all treated with CPAP and were enrolled up to 72 hours of age (median 4.1 hours, range 0.3 to 40.1hrs).This trial was also stopped after an interim analysis demonstrated a statistically significant reduction in the need for ventilation or death within seven days from 63% in the late-treated infants to 21% in early-treated infants. The median duration of ventilation in both trials was 2.5 days[20]. This study was not a prospective evaluation of early CPAP because CPAP was initiated in all infants at variable ages, and they did not evaluate infants of less than 25 weeks gestation.

Lindner et al recently reviewed their experience using a continuous prolonged (15 seconds duration) pressure controlled (20 to 25 cm H_2O) inflation of the lungs followed by continuous positive airway pressure (CPAP) of 4 to 6 cm H_2O for all ELBW infants immediately after delivery to establish a functional residual capacity (FRC) and to avoid intubation and ventilation[21]. The criteria for subsequent intubation were a $PaCO_2$ > 70 mmHg, an FiO_2 >.6 and respiratory distress with severe recurrent apnea. The rate of early intubation and mechanical ventilation in the delivery room decreased from 84% in 1994 to 40% in 1996. In 1996, 25% of the ELBW infants were never intubated (compared with 7% in 1994). There was no difference in mortality and overall there was less IVH > Grade 2 and BPD for the later cohort. No infant had an air leak upon admission to the NICU, suggesting that use of a prolonged inflation was well tolerated. Only 1 of 11 infants of 24 weeks gestation was able to avoid intubation in this study. Once again, there was no contemporaneous control group who did not receive delivery room CPAP. All of the above studies required high levels of $PaCO_2$ before initiating ventilation for this indication.

There is retrospective evidence suggesting a benefit for early CPAP in experiences from the USA. A survey of eight neonatology units in the USA in 1987 demonstrated that one unit, Columbia, had the lowest rate of CLD[22]. A more recent comparison of practices and outcomes between two neonatology units in Boston and the Babies and Children's Hospital unit (Columbia) evaluated VLBW infants born in 1991 to 1993.[23] This study revealed that 75% of infants at the Boston centers were initially treated with mechanical ventilation compared with 29% at Columbia, whereas initial CPAP was used in 63% of infants at Columbia vs. 11% at the Boston centers. Columbia also used less surfactant, 10% versus 45%, (all $p<0.001$). In addition the rates of CLD were significantly lower at Columbia compared to the other two centers (4% vs. 22%).

de Klerk and de Klerk recently published a five-year retrospective review of the outcome of 1 to 1.5 kg infants (n-116) treated with early CPAP vs. usual care (delayed CPAP)[24]. During 1996 -1998 infants were placed on CPAP within 10 minutes of admission (they did not describe the use of delivery room CPAP). Early CPAP beginning following admission to the neonatal unit decreased endotracheal intubation from 65 to 14%, $p<0.001$ and surfactant use (40 to 12%, $p<0.001$). Ventilator days were reduced from a median of 6 to 2 days ($p<0.01$) and oxygen supplementation or death at 28 days from 16 to 3%, $p<0.05$. Oxygen supplementation or death at 36 weeks did not significantly decrease (11 to 3% $p=0.25$). Ventilation and surfactant use were very high during the delayed CPAP (control period) so it is unclear whether other improvements in care may have coincided with the change to early CPAP.

Sandri et al[25] have recently published preliminary data from a multicenter randomized controlled trial of 155 infants 28 to 31 weeks gestation randomized to CPAP within 30 minutes of birth or to CPAP if the FiO_2 requirement exceeded 40%. Use of surfactant (22 to 21%, NS) and ventilator support (10 to 9%, NS) was not reduced with early CPAP. However, this trial included relatively bigger infants and the control group received CPAP at relatively low FiO_2, minimizing the difference between the experimental and control groups. This study did not evaluate the use of delivery room CPAP.

More recently Thomson et al presented the results of a multicenter trial of 237 infants from 27 to 29 weeks gestation[26], who were randomized to prophylactic surfactant followed by nasal CPAP using the Infant Flow DriverTM, early nasal CPAP followed by rescue surfactant, early IPPV with prophylactic surfactant, and conventional management. They reported that CPAP was initiated by 6 hours of age in 76% and 79% of the first 2 treatment groups, and those infants in the CPAP and rescue surfactant and prophylactic surfactant followed by CPAP groups required the lowest duration of ventilation. There were no differences in the incidence of CLD or other neonatal complications. Neither of these studies instituted the use of CPAP in the delivery room.

In a preliminary feasibility trial we have evaluated the ability of 5 sites of the NICHD Network to initiate CPAP during resuscitation, and continue its use in the NICU. In that study 103 infants were randomized to receive resuscitation with either CPAP/PEEP or no CPAP/PEEP. All infants were treated with CPAP following NICU admission. During delivery room resuscitation, 46 infants were intubated, 27 of 55 CPAP infants and 19 of 48 control infants ($p=0.33$). All 23 week gestation infants were intubated in the delivery room, irrespective of treatment group, whereas only 3 of 22 (13%) infants of 27 weeks required such intubation. When evaluated by birth weight, all 3 infants of less than 500 gm birth weight and 6 of 11 infants between 500-600 gm birth weights were intubated in the delivery room. All remaining infants were admitted to the NICU and had CPAP initiated. For infants not intubated in the DR, 36 infants were subsequently intubated in the NICU by day 7, 16 CPAP infants and 20 Control infants, ($p=0.21$). Infants in the CPAP group developed criteria for intubation sooner than the Control infants, with means and medians of 10.5 and 1.8 hours versus 20.7 and 3.3 hours,

p=0.41. These infants met criteria established for this trial which included an FiO2 > .3 to maintain an SpO2 > 90% or a PaO2 > 45 torr, an arterial PaCO2 > 55-60 with a pH < 7.25. or apnea requiring bag and mask ventilation. CPAP infants were intubated at an average FiO2 = 0.5 compared to 0.4 for control infants.

The literature thus suggests that early CPAP may be of substantial benefit, although none of this information has been obtained from prospective randomized trials of CPAP randomly applied in the delivery room to a population of VLBW or ELBW infants, with an appropriate control group. The terms early CPAP in the above studies (apart from that of Lindner et al[15]) involved the application of CPAP shortly following birth, not immediately after delivery. It is not surprising, therefore, that the recent revised NRP guidelines do not mention the use of CPAP/PEEP for neonatal resuscitation.[27] There is also some evidence that the level of CPAP needed may vary depending on the actual device utilized. Pandit et al and Courtney et al have demonstrated that variable flow CPAP was associated with a lower work of breathing and increased compliance at all levels of CPAP whereas constant flow nasal CPAP increased compliance only at 8 cm H2O.[28] In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.[29] A more recent trial compared the use of variable flow CPAP to conventional CPAP at extubation for 162 ELBW infants and reported no significant differences with either form of CPAP.[30] This study noted that 40% of ELBW infants failed extubation primarily because of apnea.

There are no studies in the surfactant and antenatal steroid era which have prospectively compared delivery room, CPAP with a more conventional approach, such as the use of prophylactic surfactant and conventional ventilation. The current available evidence demonstrates that prophylactic natural surfactant treatment significantly decreases mortality, air leak, and BPD in preterm infants.[31] Early surfactant, defined as surfactant at less than 2 hours of life is also of benefit and reduces air leaks, and mortality.[32] These reviewers noted that "early surfactant administration significantly reduces the risk of key clinical outcomes including pneumothorax, PIE, chronic lung disease, and neonatal mortality. Given the efficacy of prophylactic surfactant therapy (Soll 1999), this meta-analysis suggests that early selective surfactant administration to intubated infants with early signs of RDS may be part of a clinical spectrum of improved outcomes with earlier treatment". The most recent experience regarding early surfactant was presented by Horbar et al at the SPR in May, 2003. Their study which involved a cluster randomization in 57 NICUs of a practice to administer surfactant earlier compared with 57 control NICUs. They noted that infants at the intervention sites received their surfactant more often in the DR (54.7 vs 18.2%, p < 0.001) and earlier than the control sites (21 vs 78 minutes, p <0.001). There were no differences in mortality and pneumothoraces, the intervention centers had a lower rate of overall and severe IVH (28% vs 33%, p < 0.04, 10% vs 14%, p < 0.001) which were secondary outcomes of this trial.[33]

The most recent published study by Tooley and Dyke evaluated the use of prophylactic surfactant and early extubation to CPAP versus prophylactic surfactant and continuing management.[34] In this study 42 infants of 25 to 28(+6) wk of gestation were intubated at birth and given one dose of surfactant. They were then randomized within one hour of birth to either continue with conventional ventilation or to be extubated to nCPAP. They reported that 8 out of 21 (38%) babies randomized to nCPAP did not require subsequent re-ventilation. (Ventilation rates of 62% vs 100%, p = 0.0034). The smallest baby successfully extubated weighed 745 g. There were also significantly fewer infants intubated in the nCPAP group at 72 h of age (47% vs 81%, p = 0.025). There was no significant difference between the two groups in the number of babies that died, developed chronic lung disease or severe intraventricular hemorrhage. This study demonstrates that a significant number of very preterm babies with RDS can be extubated

to nCPAP after receiving one dose of surfactant. The current SUPPORT study will address this population, extended to 24 weeks, using a similar methodology for the infants of 24 to 27 6/7ths weeks who fail initial CPAP, with adequate power to determine if this approach is associated with significant benefits in terms of important short and longer term clinical outcomes.

Oxygen Saturation:

There is now an emerging body of information that suggests that many of the morbid conditions associated with extreme immaturity are potentiated by an excess of free-radicals occurring in infants who are intrinsically deficient in antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase. During hypoxia, metabolic alterations prime hypoxic cells to produce free oxygen radicals when subsequently exposed to oxygen. Such reperfusion injury, in addition to increasing the production of free oxygen radicals, is associated with other metabolic changes which may produce long lasting harmful effects. Silvers et al reported that a low plasma antioxidant activity at birth in premature infants was an independent risk factor for mortality.[35] Pulmonary oxygen toxicity, through the generation of reactive oxygen/nitrogen species in excess-of antioxidant defenses, is believed to be a major contributor to the development of BPD.[363738] For example the preterm macrophage showed a significant increase in cytokine mRNA and protein after overnight incubation in 95% oxygen compared with cells from term animals. Only macrophages from premature animals had a significant increase in intracellular oxygen radical content, measured by 2', 7'-dichlorofluorescin analysis, after incubation in 95% oxygen. This enhanced inflammatory cytokine response to oxygen has been postulated to be a mechanism involved in the early development of chronic lung disease in premature infants.[39] Varsila et al noted that immaturity is the most important factor explaining free radical-mediated pulmonary protein oxidation in premature newborn infants and that oxidation of proteins is related to the development of chronic lung disease.[40]

There are a number of prospective randomized trials that have compared the use of room air with 100% oxygen for neonatal resuscitation, and these have reported Infants resuscitated with room air resumed spontaneous breathing faster and required less positive pressure ventilation than infants resuscitated with oxygen.[41 42] Vento et al also demonstrated that that infants resuscitated with oxygen demonstrated long lasting evidence of oxidative stress and activities of superoxide dismutase and catalase in erythrocytes that were 69% and 78% higher, respectively compared with control infants resuscitated with room air at 28 days of postnatal life.[43] A recent meta-analysis of room air vs 100% oxygen resuscitation comprising of 1,693 infants in five trials revealed decreased neonatal resuscitation in infants resuscitated with room air (6 vs 11%, $p<0.005$ or 0.57 (95% CI 0.40 – 0.81))[44]. While these studies described results of mostly term infants, some infants were premature and the premature infant is known to have decreased antioxidants which would increase their susceptibility to oxygen toxicity. In the only randomized prospective trial to evaluate room air compared with oxygen in preterm infants, Lundstrom et al resuscitated infants of less than 33 weeks gestation who were randomized to receive either 80% oxygen or room air and noted that 2 hours following delivery, the room air infants had a higher cerebral blood flow compared with oxygen resuscitated infants. (median (interquartile range)): 15.9 (13.6-21.9) v 12.2 (10.7-13.8) ml/100 g/minute).[45] They did not find any significant differences in short or long-term outcomes but did note that SpO2 was lower in the room air infants with values at 5 and 7 minutes of 75% and 80% compared with 92% and 94% in the 80% oxygen group ($p<0.001$). Current monitoring with pulse oximetry using limits of 95 to 96% will result in significant periods wherein the infants actual PaO2 may increase to very high levels, as there are rapid increases in PaO2 with very small increments in SpO2 at this plateau portion of the hemoglobin dissociation curve.

Tin et al retrospectively reviewed outcomes for infants admitted to various neonatal intensive care units in northern England from 1990 to 1994 and managed with lower (70-90%) or higher SpO2 ranges (88%-98%).[46] They reported that infants who were managed for at least the first 8 weeks of life with SpO2s from 88-98% developed retinopathy of prematurity severe enough to be treated with cryotherapy four times as often as infants managed with the lower SpO2 ranges. Infants managed with the lower SpO2 ranges did not have increased risk of mortality or neurodevelopmental impairment. Bancalari et al using transcutaneous oxygen monitoring were able to show that infants who received continuous monitoring had a similar incidence of ROP to infants who were monitored by intermittent sampling had similar incidences of ROP, however for subgroup of infants $\geq$ 1100gm, there was a decrease in the incidence of ROP.[47] The STOP-ROP trial randomized infants with already established pre-threshold retinopathy and an SpO2 less than 94% to two ranges of SpO2 (89% to 94% versus 96% to 99%), for at least 2 weeks and until both eyes were at study endpoints. The higher range of SpO2 was associated with a non-significant decrease in the progression of ROP, but was associated with a greater need for oxygen and more exacerbations of BPD.[48]

Chow et al reported their observations following the institution in 1993 of a detailed oxygen management policy that included strict guidelines in the practices of increasing and weaning of fraction of inspired oxygen (FIO2) and the monitoring of oxygen saturation parameters in the delivery room, during in-house transport of infants to the NICU, and throughout hospitalization.[49] The main objectives were to avoid hyperoxia and repeated episodes of hypoxia-hyperoxia in very low birth weight infants. Their approach was initiated at birth, and included the avoidance of repeated increases and decreases of the FIO2, and a change in previously used alarm limits. They reported that following the implementation of these new management strategies that the incidence of ROP Grades 3 to 4 decreased consistently in a 5-year period from 12.5% in 1997 to 2.5% in 2001 and that the need for ROP laser treatment decreased from 4.5% in 1997 to 0% in the last 3 years. They adopted an SpO2 range of 85% to 95% for infants > 32 weeks gestation at birth, and a range of 85% to 93% for infants < 32 weeks. In addition some of their faculty used a range of 83% to 93%. This study did not provide any prospective values of the actual SpO2 ranges that were actually achieved in their infants, and thus it is uncertain whether their observed reductions in ROP were related to the altered SpO2 changes, or to overall changes in management over the period of the study. While these observations are encouraging, the authors did not report the complete neurodevelopmental outcomes for the infants cared for during the period of the new oxygen guidelines, and in the absence of contemporaneous controls, these results cannot be considered as proof that the SpO2 ranges used by this group are beneficial in terms of significant longer -term neurodevelopmental outcomes.

The most recent trial conducted in Australia compared SpO2 ranges of 91% - 94% versus 95% - 98% in 358 infants of less than 30 weeks who remained oxygen dependent at 32 weeks. The primary outcomes were growth and neurodevelopmental measures at a corrected age of 12 months. The high-saturation group received oxygen for a longer period after randomization (median, 40 days vs. 18 days; P<0.001) and had a significantly higher rate of dependence on supplemental oxygen at 36 weeks of postmenstrual age and a significantly higher frequency of home-based oxygen therapy. but resulted in an increased duration of oxygen supplementation.[50] They reported that additional oxygen supplementation did not improve survival, growth, or the occurrence of cerebral palsy at 18 to 24 months. Anderson et al have recently reported the results of a survey of pulse oximetry practices in 142 NICUs in the USA and noted a wide range of monitoring limits from 82% to 100%. They reported a lowered rate of ablative eye surgery in units that used lower maximal SpO2 limits, with the lowest range seen in units that had a maximum SpO2 of < 92%.[51]

In a recent review of oxygen toxicity in the premature infant Weinberger et al recommended that a strategy of limiting oxygen supplementation should be explored to reduce significant morbidities in the premature infant.[52] No studies to date have prospectively randomized ELBW infants to differing oxygenation ranges from birth onwards to determine if there is a benefit of lower versus higher saturation ranges.

1.5 Recent Relevant Studies

We have recently evaluated an FDA approved device specifically designed to facilitate neonatal resuscitation (Neopuff Infant Resuscitator, Fisher and Paykel, Auckland, New Zealand). This device has a t-piece that attaches to a mask and to a simple pressure generator. The inspiratory pressure can be set to a determined level, and a twist valve at the top of the t-piece determines the end-expiratory pressure. Most operators, with the exception of experienced respiratory therapists cannot routinely deliver a predetermined level of positive inspiratory pressures and PEEP[53] using an anesthesia-type manual bag and a neonatal manikin. In contrast, all operators could deliver the predetermined pressures with little intra-individual variation using the Neopuff®. The device operates identically using either a mask or endotracheal tube connection with or without PEEP/CPAP and the operator can adjust the positive inspiratory pressure (PIP) manually during resuscitation. At a flow of 10 liter per minute (lpm) or less, the maximum inadvertent CPAP/PEEP is 0.5 cm H_2O; which does not increase up to rates of 80 breaths per minute, the highest tested rate. The wave form is square, and is more similar to ventilator wave forms than to wave forms obtained using an anesthesia device. It should be noted, that the standard anesthesia devices used in delivery rooms may not deliver the desired CPAP/PEEP, depending on the operator's experience and skill, and may result in overshooting the desired PIP, even when the device is used by experienced operators. The Neopuff® device is now used as the standard resuscitation device in a number of hospitals in the USA, including at least two units in the NICHD Network.

There has been a recent trial evaluating earlier criteria for retinal laser ablative surgery for ROP, the ETROP study.[54] This study has demonstrated that using such criteria the visual outcomes are improved and reported that grating acuity results showed a reduction in unfavorable visual acuity outcomes with earlier treatment, from 19.5% to 14.5% (P=.01)and that unfavorable structural outcomes were reduced from 15.6% to 9.1% (P<.001) at 9 months. They recommend retinal ablative therapy for eyes with type I ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph); zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 ROP with plus disease. While these results are likely to be integrated into Network practice, there is currently no baseline data regarding the number of infants who would meet these criteria, and thus we will utilize the presence of Stage 3 or greater ROP and/or the receipt of retinal surgery to power our current trial.

2.1 Study Design

This will be a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. The individual factors to be tested will be:

1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early ($\leq$ 1 hour) surfactant and mechanical ventilation.

2) A prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant is no longer requiring ventilatory support

or oxygen.

The oxygen saturation monitoring portion of our study will be designed to parallel the planned POST-ROP trial, a multicenter, multinational prospective trial to evaluate different SpO2 levels from birth.[55] The methodology described under oxygen monitoring (**Section 4.1B**) was developed for the current protocol to allow a blinded comparison of 2 different SpO2 levels using specially designed pulse oximeters. These devices have been developed by the Masimo Corporation (Irvine Ca) and tested prior to initiation of this trial, and the POST-ROP study group has agreed to use the ranges described in this protocol, and the methodology that will allow the oximeters to provide actual SpO2 values when the SpO2 is < 85% and > 95%(Personal communication, Cynthia Cole 2004). This methodology will provide the clinicians and caretakers with the infants' actual SpO2 values during hypoxia and hyperoxia, within the current parameters of clinically accepted practice.

Please see **Section 8.2** for further Tables describing details regarding the projected outcomes relative to the study interventions

Randomized Intervention	**Low SpO2 85% to 89%**	**High SpO2 91 to 95%**
Treatment **Early CPAP**	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control **Prophylactic/Early Surfactant**	Control + Low SpO2	Control + High SpO2

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

2). We hypothesize that that relative to infants managed with a higher SpO2 range that the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

2.3 Secondary Hypotheses

We hypothesize that the use of continuous positive airway pressure (CPAP) with a permissive ventilator strategy and/or a lower SpO2 range starting at birth in the delivery room will result in the following:

- A decreased Mortality/NDI at 18-22 months corrected age.

- A decreased frequency of endotracheal intubation before 10 minutes of age
- A decrease of the total duration of mechanical ventilation during the entire NICU stay
- A decreased incidence of surfactant treatment
- A decreased incidence of air leaks on admission and overall
- A decreased duration of intubation
- A decreased duration of mechanical ventilation
- A decreased duration of oxygen supplementation
- A decreased duration of the percentage of pulse oximetry values > 90%
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- A decrease in the percentage of infants who receive postnatal steroids to prevent or treat BPD
- A decreased incidence of BPD at 36 weeks using the physiologic definition of BPD
- A decreased incidence of ROP or Stage 3 ROP
- A decreased incidence of necrotizing enterocolitis (NEC)
- A decreased incidence of IVH and severe IVH
- A decreased incidence of periventricular leukomalacia
- A decreased incidence of neurodevelopmental impairment at 18-22 month follow-up
- A decreased incidence of cerebral palsy at 18-22 month follow-up

3.1 Study Population

Study subjects are infants of 24 0/7ths to 27 6/7th weeks at birth for which a decision has been made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) will be enrolled because over 80% of such infants in the Network are intubated, usually early in their neonatal course. It is important to note that previous studies have included few, if any infants less than 25 weeks gestation and such infants are not included in the current COIN trial or the proposed Vermont Oxford Trial. Such infants will be enrolled in this trial because they are the group of infants with the highest mortality and morbidity. The feasibility trial demonstrated that the 5 NICHD centers involved could reduce intubation in the delivery room to less than 50% of such infants if they are not intubated for surfactant. We will exclude infants of 23 weeks or less in view of their extremely high mortality and morbidity, and their almost universal need for delivery room intubation for resuscitation. We have included Tables at the end of the protocol utilizing infants from 23 to 28 weeks to demonstrate that our sample size estimates will not be adversely affected if we should choose to include infants of 23 and/or 28 weeks.

Strata: There will be 2 randomization strata, infants of 24 0/7ths to 25 6/7ths weeks, and infants of 26 0/7ths-27 6/7ths weeks by best obstetrical estimate. The purpose of stratification is to assure an appropriate distribution of risk among the four study arms. The study will not be powered to detect outcome differences between strata.

3.2 Inclusion Criteria

- Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
- Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Infants whose parents/legal guardians have provided consent for enrollment, or
- Infants without known major congenital malformations

3.3 Exclusion Criteria

- Any infant transported to the center after delivery
- Infants whose parents/legal guardians refuse consent
- Infants born during a time when the research apparatus/study personnel are not available
- Infants < 24 weeks 0 days or ≥ 28 weeks 0 days, completed weeks of gestation

3.4 Sampling Recruitment and Screening Procedures

Infants will be recruited for this study by approaching one or both parents at the time of admission to the hospital where there is deemed to be a risk of premature delivery at 27 6/7ths weeks or less.

3.5 Screening Procedures

All admissions for threatened premature delivery will be screened on a daily basis to ensure that eligible patients can be enrolled. We will inform our obstetrical colleagues at each involved institution of the nature of this study, and encourage them to discuss this study with their patients at risk of premature delivery. The study coordinator at each site will maintain a screening log of potentially eligible patients. In addition the usual practice of neonatal consultation for all such at risk deliveries will provide a second opportunity to approach mothers with fetuses at risk of preterm delivery

3.6 Other Procedures

A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology will be used at all sites for the delivery room administration of CPAP. A training video to explain the proper use of the Neopuff® will be provided to any site which wishes to use it and is not familiar with the device.

3.7 Randomization

Randomization will be stratified by gestational age group, will occur prior to delivery for consented deliveries, and will be performed by utilizing specially prepared double-sealed envelopes. Deliveries will be randomized as a unit, thus multiples, twins, triplets etc will be randomized to the same arm of the trial. We believe that this methodology will improve the percentage of consents, since in previous trials parents of multiple infants have expressed concern that their infants were being randomized to different treatment arms. We have made an appropriate sample size adjustment to account for this clustering effect.

Each randomization will indicate either Treatment Group (CPAP and permissive ventilation management) or Control Group (Prophylactic/Early surfactant and conventional ventilator management) and either the Low (85%-89%) or High (91% - 95%) SpO2 group. Parents will be approached for consent before delivery, but the randomization envelope will only be opened when delivery is imminent for a consented family.

The Pulse Oximeters (PO) will have unique identifying labels and the oximeter specified in the randomization will be identified by a unique number which will match the number of the study Pulse Oximeter assigned for that infant. All caretakers including the coordinators will be blinded to the Pulse Oximeter range, and an identification code for each site will be maintained by the PI/Site Coordinator should identification be required for patient safety. RTI will work with Masimo to ensure that the POs are labeled with unique identifiers, whose code will identify the

actual range of the individual PO. These would be affixed prior to shipping to the sites, and a copy of the labels sent to the site would be provided to RTI.

This methodology should reduce the work load to the sites at the time of randomization, providing the care team with the information needed for the infants' randomization, and will allow the study center to be notified within 24 hours of any randomization.

3.8 Informed Consent:

Parents will be approached prior to delivery for informed consent, and their infants enrolled at delivery. As previously noted we will randomize by family, thus all offspring will be randomized to the same trial arms, provided adequate equipment and personnel are available at the time of delivery.

3.9 Management and Retention of Study Population

All enrolled infants will be seen at follow-up-up at 18 to 22 months corrected age. We do not anticipate a significant loss other than death (13% in the first 12 hours , approximately 32% before discharge, based on year 2000 registry data), and will plan for a further 15% attrition.

4.1 A: Study Intervention: Mode of Ventilatory Support

The intervention will begin after birth when the infant is given to the resuscitation team. The conduct of the resuscitation will follow usual guidelines, and once stabilized, all Control infants in both strata will receive prophylactic/early surfactant (within 1 hour of age) whereas all Treatment infants will be placed on CPAP/PEEP following stabilization, and be intubated only for resuscitation indications.

The assignment to either a high or low SpO2 by study oximeter assignment will be performed immediately following NICU admission, with a maximum allowable delay of 2 hours following NICU admission.

TREATMENT: CPAP Group : Early Extubation and CPAP

Delivery Room Management

FiO2:

Standard of care.

CPAP:

CPAP or ventilation with PEEP will be utilized if the infant requires positive pressure during resuscitation. CPAP will be continued until admission to the NICU using the Neopuff or equivalent device and a face mask or nasal prongs. Initial PPV will be at a PIP of 15-25 cm H_2O and a PEEP/CPAP of 5 cm cmH_2O.

Intubation:

Infants may not be intubated for surfactant only in the DR. Infants who require intubation for resuscitation will receive surfactant within 60 minutes of birth.
Intubation will be performed only for the standard NRP indications including failure to respond to PPV with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determines that surfactant is urgently required.

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

NICU Management

These infants will be managed on nasal CPAP, and intubation is never required by protocol. They *MAY* be intubated if they meet ***ANY*** *of* the criteria listed below. If intubated within the first 48 hours of life they should receive surfactant

Intubation:

- An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) documented on a single blood gas within 1 hour of intubation
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation.)

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

These criteria will continue in effect for a minimum of 14 days of life.

Intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.
(e.g. - Upper airway obstruction (choanal atresia, micrognathia/glossoptosis)).

Extubation:

An intubated CPAP-Treatment infant ***MUST*** *have extubation attempted within 24 hours if* **ALL** *of the following criteria are met and documented on a single blood gas*

- $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples)
- An indicated SpO2 $\leq$ 88% with an FiO2 $\leq$ 50%
- A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving ionotropic/vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA

These criteria will continue in effect for the first 14 days of life.

Failure to extubate an infant meeting all of the above criteria will be recorded as a study protocol violation unless extenuating circumstances are noted. (e.g. - PIE, airleak)

Reintubation

If a Treatment infant is extubated as per Protocol Criteria, and requires re-intubation for any indication, any further attempt at extubation may be delayed for 24 – 48 hrs based on the clinician's decision.
Re-intubation criteria are the same as those for Intubation for the CPAP infants. Thus, intubation is not required, but these infants **MAY** be reintubated if they meet **ANY** of the following:

Re-Intubation Criteria:

- An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) for 2 successive blood gases at least 15 minutes apart.
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation as noted above on page 13)

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Re-intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.

D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be discontinued earlier and follow unit Standard of Care. CPAP may be restarted at any time in such infants.

CPAP infants who require intubation three times, for any criteria, will have all subsequent treatment including subsequent extubations and any further re-intubations performed using unit Standard of Care. This addition is to prevent such infants from being exposed to further protocol driven intubations and extubations.

Surfactant

Infants intubated in the first 48 hours for respiratory distress should be given a minimum of one dose of surfactant
Up to 4 surfactant administrations may be given if the FiO2 is greater than 50% following manufacturers' recommendations for dose and dosing interval.

Explanation:

The purpose of the above criteria is to minimize the duration of intubation of Treatment infants. The Criteria for extubation are more severe than those of the Control Group infants, and extubation must be attempted for any infant who fulfills the stated criteria.

The criteria for re-intubation recognize that intubation is traumatic, and is designed to avoid frequent attempts at extubation for infants who fail.

CONTROL- Prophylactic/Early Surfactant and Ventilation

Delivery Room Management:

Infants will be intubated in the delivery room and given surfactant or receive surfactant

within 60 min minutes of birth. The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

NICU Management:

:

***Extubation*:**

An intubated Surfactant-Control infant will continue to receive mechanical ventilation until extubation criteria are satisfied, but **MUST** have Extubation attempted within 24 hours of fulfilling ***ALL*** of the following criteria documented on a single blood gas.

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 = 35 with a SpO2 > 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving ionotropic / vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA (Defined as bounding pulses, audible murmur and Echo confirmation of L-R shunting with increased LA/Ao size

These criteria will continue in effect for a minimum of 14 days for all infants.

Failure to attempt to extubate an infant meeting all of the above criteria, or extubation prior to reaching criteria, will be recorded as a study protocol violation unless extenuating circumstances are noted.

Weaning

This protocol will not define strict weaning criteria for the Control infants, but it is to be understood that reasonable attempts should be made to extubate these infants. While it is understood that some centers may be using somewhat more severe FiO2 and PaCO2 criteria than those listed here as current practice, these Criteria are thought to reflect current Network practice and practice at 2 of the 3 Best practice centers.

Reintubation:

- Control Infants may be reintubated using Standard of Care.

Explanation:

Control infants are to be treated using an approach considered similar to current standards of care. Apparatus for resuscitation for Control Infants at each center will represent their usual equipment for the resuscitation of an ELBW infant. The Neopuff may be utilized for such infants as above, but this is not mandatory. It is anticipated that the majority of these infants will be intubated and receive surfactant in the delivery room.

4.1 B: Study Intervention: Low versus High SpO2 Range:

There will be 2 ranges of SpO2 utilized during this trial. The Low target range will be 85% to 89% and the High target range will be 91% to 95%. The altered Pulse Oximeters (PO) are described below, and will display a range of 88% to 92% when the SpO2 ranges are in the Target ranges indicated above. Thus a Low range PO will read 88% when the actual SpO2 is

approximately 86%, and 92% when the actual SpO2 is 89%. Similarly the High range PO will display 88% when the actual SpO2 is 91% and indicate 92% when the actual SpO2 is approximately 95%. See below for further explanation. This deviation is similar to the BOOST trial which used a continuous 3% offset.[42] As an added safety feature, the POs used in this trial will revert to the actual SpO2 values and allow the caretakers to be aware of actual SpO2 values < 85% and > 95%.

Low Range Infants:

These infants will be monitored with a target SpO2 range of 85% -89% with suggested indicated alarm limits of 85% and 95%, representing approximately a 10% span for alarms as long as the infants are receiving any ventilatory support, CPAP, and/or supplemental oxygen. **The study pulse oximeters will be applied to the infant within two hours following NICU admission.** The assigned PO will remain on the infant and will be removed once the infant has been in room air and off ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA

High Range Infants:

These infants will be monitored with a target SpO2 range of 91% -95% with suggested indicated alarm limits of 85% to 95% representing approximately 10% span for alarms as long as they are receiving any ventilatory support, CPAP and/or supplemental oxygen. The study pulse oximeters will be removed once the infant has been in room air for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA

These interventions will be delivered using specially developed pulse oximeters whose displays (the actual readings seen by caretakers) will be adjusted so that the randomized range of SpO2 (either 85%-89%, or 91%-95%) will be indicated by a range of 88%-92%. This is done by progressively altering the offset as the alarm limits are approached, and Masimo has confirmed that this technology is workable. The target oxygen saturation (88-92%) of the display will be the same in both groups as indicated in Table1 below.

These POs will be able to display trend plots of the SpO2 display for a preceding interval to allow the caretakers to receive feedback regarding the actual SpO2 ranges of their baby.

The suggested alarms limits will be 84% and 96% for both groups.

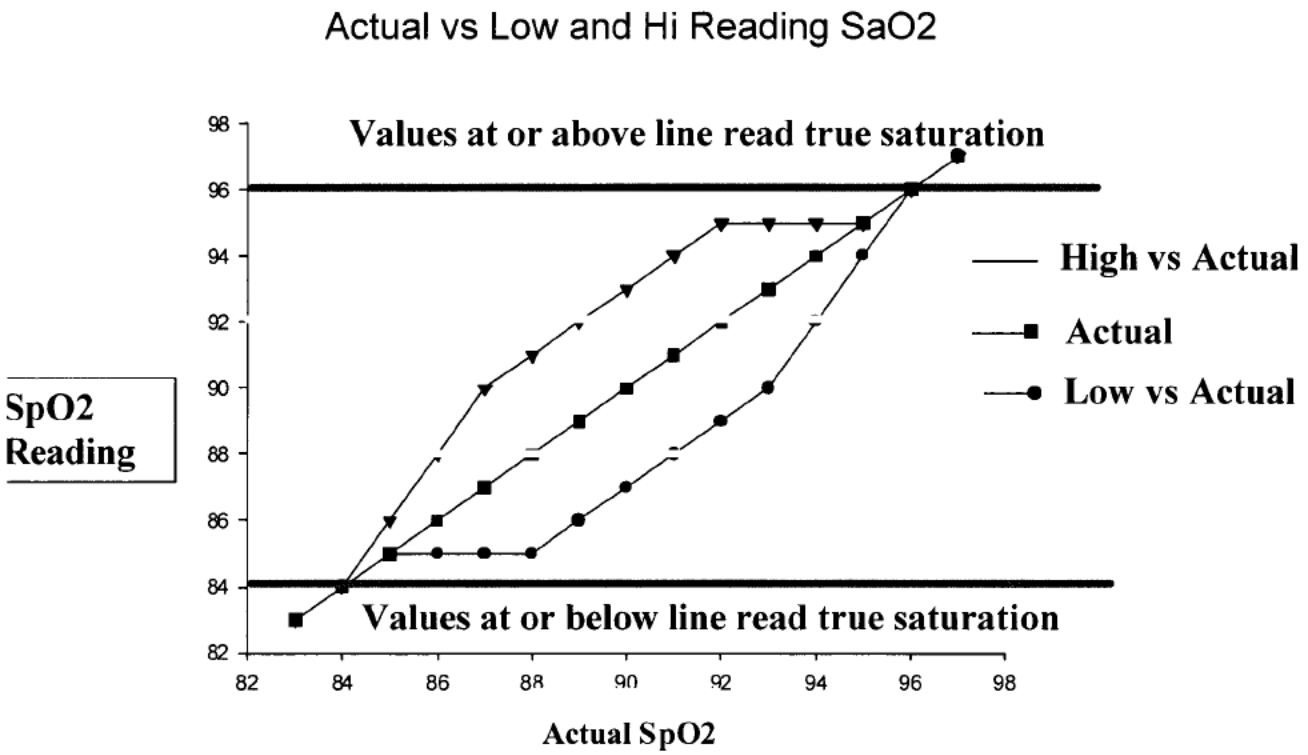
Table 1. Output and Actual SpO2 Targets and Alarms

SpO2 Group	Displayed Target	Actual Target	Alarm Values
Low SpO2	88-92%	85-89%	<85 and >95%
High SpO2	88-92%	91-95%	<85 and >95%

The pulse oximeters will display the actual reading when then the SpO2 is below 85% and above 95%. This will provide for an overall set of limits on actual SpO2 of 84% to 96% which we believe will avoid unacceptable levels of hypoxia, (< 85%) and hyperoxia (> 95%) **All data below 85% and above 95% will be unaltered on all oximeters**. An averaging time of 16 seconds will be applied in keeping with the settings used by POST-ROP. The preset alarm

delay will be 10 seconds. The fail-safe alarm will alarm whenever the reading is 5% below the low alarm limit, in the study this will be at 80%. Some network centers use an averaging interval of 30 seconds, others use very short averaging times. This setting will allow for appropriate response times without unmasking the caretakers.

We believe that this methodology will provide an acceptable ethical design for this trial. The diagram below demonstrates how the pulse oximeter readings are altered between values of 85% to 95%. Readings below or above these levels will not be altered, and will represent actual SpO2 as determined by the pulse oximeter. Note that the entire range of actual SpO2 is altered to either a lower (Low SpO2 Group) value or higher value (High SpO2 Group) till the ends of the alarm ranges of 85% and 95% which will ensure that the infants SpO2 will be separated throughout this range.



Every 30 days until 36 weeks PCA or until the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per 10 seconds of monitoring) will be downloaded and transmitted to RTI for subsequent analyses. (This interval of sampling may change to a less frequent interval for the convenience of the study personnel, without losing significant data). These data points will be used to confirm that the infants were managed at the target ranges and provide objective confirmation of the SpO2 Group assignments. The technology for downloading and interpreting this data was used in the DR CPAP Pilot trial, but recent technology utilizing a software program (Profox, Profox Inc, Escondido, Ca) which has been written to facilitate this process, will dramatically simplify this procedure.

Non-study pulse oximeters cannot be used on enrolled patients. If a second oximeter is

required for such a patient, the site coordinator will provide an identical oximeter for the patient.

All ventilatory care after 14 days of age will follow the standard of care for each unit. Each unit will provide guidelines for their approach to continuing mechanical ventilation.

4.2 Delivery of Interventions

CPAP/PEEP in the DR

CPAP and positive pressure ventilation (PPV) in the delivery room for Treatment infants will be administered via a T-piece resuscitator, a neonatal ventilator or an equivalent device that is currently used by the site for the delivery of CPAP. (See **3.6**).

Use of Nasal SIMV;

This approach is currently used by some Network units and has been previously established as being superior to CPAP following extubation in three prospective trials.[56,57,58] For uniformity nasal SIMV may be used in place of CPAP ***only following extubation for both Treatment and Control infants.***

Use of Caffeine:

Caffeine may be administered 2 hours prior to planned extubation, and for any clinically significant apnea.[59]

Surfactant Type:

All centers are asked to follow current unit practice in determining the type of surfactant utilized, and manufacturers' recommendations for redosing intervals.

The protocol requires that at least one dose of surfactant be administered to any infant intubated within 48 hours of birth, with evidence of respiratory distress, who has not previously received surfactant.:

Postnatal Steroids

Postnatal steroids for the purpose of preventing or treating BPD/CLD will be prohibited for any infant in this trial in the first 21 days of life. Hydrocortisone for hypotension may be used as noted below.

If postnatal steroid use is considered after 21 days of life for any infant for the prevention/treatment of established lung disease the following guidelines should be followed:

1. The AAP statement and recommendations regarding Post-natal steroids should be adhered to.[60]
2. The lowest dose of dexamethasone considered effective should be used and if ineffective after 24 – 48 hours they should be stopped.
3. Consider using hydrocortisone as a first therapy at a dose of 1 -2 mg/kg/day before using dexamethasone.
4. For hypotension, hydrocortisone in a dose of 1 mg/kg/dose should be given after fluid administration and standard doses of ionotropes/pressors have failed to correct the low blood pressure.

Head Ultrasound

If a Head ultrasound is done between days 4 and 21 the results will be recorded for this study. If one is not done for standard of care, the study requires that at least one HUS be completed during this window

4.3 Protocol Violations:

The occurrence of any one of the following criteria will determine whether an individual infant will be considered a protocol violation:

1. Intubation of a treatment group infant in the DR for the exclusive purpose of giving surfactant, in the absence of bradycardia (HR< 100 bpm) and/or poor color or an SpO2< 85-90% in an infant with adequate spontaneous respirations or receiving adequate ventilation
2. Failure to continue CPAP on admission to the NICU for a treatment infant requiring supplemental oxygen
3. Intubation and surfactant administration of a treatment infant without meeting stated protocol criteria.
4. Failure to extubate a Treatment infant who fulfills all the extubation criteria.
5. Extubation of a Control infant who does not meet any of the Extubation criteria.

All protocol violations will be reviewed by the center PI who will discuss each protocol violation with the involved clinicians and provide a written summary including steps taken to avoid future violations.

4.4 Adverse Events

Serious and unanticipated adverse events may be anticipated in this vulnerable population. Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

These outcomes will be evaluated on a monthly basis by RTI, and if the incidence of any of these outcomes is determined to be 5% - 10% greater in any arm of the study, this information will be provided to the Study PI and committee and the DSMC for immediate consideration, and evaluated for consideration of termination of the study or treatment arm.

4.5 Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. Obrien-Fleming [61] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock [62] boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

5.1 Measurement Methods:

The PO stored data will be retrieved using a routine provided to all site coordinators, and the resultant data file will be sent electronically to RTI to be included as part of the study data collection.

5.2 Schedule of Data Collection: (See Data tables in Appendix A)

5.3 Primary and Secondary Outcome Measures

5.3.1 Primary Outcome Measure

The primary outcome will be the percentage of infants surviving without BPD (using the Physiologic Definition) or severe ROP (threshold disease or the need for surgery).

5.3.2 Secondary Outcome Measures

- The five minute Apgar score
- The percentage of infants with death or neurodevelopmental impairment at 18 months
- The total duration of mechanical ventilation during the entire NICU stay
- The percent of infants alive and off ventilation by day 7
- The proportion of infants receiving surfactant treatment
- The incidence of air leaks on admission and overall
- The incidence of BPD at 36 weeks using the physiologic definition of BPD
- The incidence of death
- The proportion of infants with severe IVH
- The proportion of infants with PVL
- The proportion of infants with threshold ROP and requiring surgery for ROP
- The proportion of infants requiring endotracheal intubation before 10 minutes of age
- The proportion of infants with of air leaks on admission and overall
- The duration of oxygen supplementation
- The percentage of pulse oximetry values > 90%
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- The proportion of infants who receive postnatal steroids to prevent or treat BPD
- The proportion of infants with who develop necrotizing enterocolitis (NEC)
- The proportion of infants with cerebral palsy at 18-22 month follow-up

6.1 Training Study Personnel

6.1.1 Job Descriptions of Study Personnel

The NICHD coordinators will assist the respiratory therapists in each unit regarding the set up the equipment for the delivery of CPAP in the delivery room, and in the NICU.

6.1.2 Training of Personnel

There will be a training session held in Cincinnati about the delivery of CPAP in the delivery room and in the NICU, and a review of available devices that may be used for this intervention.

7.1 Data Collection and Management

We will develop the required CRFs as per Network procedures. It will be our aim to minimize these to ensure that data is collected regarding the intervention, the adherence to the protocol for intubation, surfactant administration, and extubation, and the occurrence of the primary and secondary end-points. All remaining information will be extracted for the current data forms.

8.1 Statistical Analysis

8.1.1 Analysis Plan

The primary analyses of this factorial trial will be a logistic regression analysis of the percent of each Group (Treatment vs Control, High vs Low SpO2) who developed their respective outcome measure (survival without BPD or ROP at 36 weeks respectively). An important analysis of a secondary outcome will determine if there is an effect of the interventions on the percent infants who survive without neurodevelopmental sequelae at 2 years For all secondary outcomes, univariate analysis for continuous variables will be performed using parametric (e.g., Student t tests, ANOVA), and non-parametric (e.g., Mann-Whitney U) tests where appropriate; categorical variables including the primary outcome, feasibility, will be examined by Chi square analysis. Analysis of covariance and multiple regression models will be used to examine the interaction between, and the independent effects of, various factors, (e.g., birth weight, gestational age, gender, treatment group, center, etc.) upon secondary outcomes (i.e., time to improvement in oxygen saturation, duration of positive pressure ventilation, five minute Apgar score, duration of mechanical ventilation, surfactant requirement, incidence of air leaks, and incidence of BPD).

8.2 Sample Size

As discussed above, there are two main outcomes for the factorial design: mortality or BPD; mortality or ROP. Mortality or NDI is a secondary outcome. For the cohort of infants born in 2000, 401-1000g birth weight, we have the following prevalence of outcomes for four subgroups of that cohort: Please note that we used population groupings to include or exclude infants of 23 and 28 weeks. These additional groups do not change the sample size estimates as the outcomes are essentially similar.

Subgroup	Death/BPD	Death/> Stage III ROP	Death/NDI
23-27 GA	70.6	53.1	65.7
24-28 GA	64.8	44.5	59.3
24-27 GA	66.6	46.8	60.7
23-28 GA	68.6	50.4	64.0

If the study is powered for the two outcomes, Death/BPD and Death/>Stage III ROP, then the sample size is driven by the prevalence nearest 50% for a given absolute percentage detectable change in the outcome. In this case it's the Death/>Stage III ROP outcome with a range of 44.5% to 53.1% across the subgroups. Furthermore, the sample size depends on the outcome rate only through the standard deviation of the rate and this turns out to be essentially

50% for all subgroups (i.e. ranges from 49.7% to 50.0%). Hence one sample size table suffices for all.

Hence, for any of the four groups the table below gives the total sample sizes required for a range of absolute percent changes, a two-tailed alpha level test of 5% and for powers of 80% and 90%. The N1 column powers the 2 x 2 factorial for the two primary outcomes and the N2 column assures comparable power for the Death/NDI outcome.

With regard to the power for detecting the interaction between the two factors in the factorial, a fourfold increase in the stated sample size would be required to detect an interaction effect as large or larger as that stated in the table (i.e. the Detectable Difference), assuming the same alpha level and power. The interaction effect referred to is the classical one where the difference in outcome for one of the treatments in the factorial differs according to the level of the other treatment (i.e. the treatment effects are not additive).

If the study is powered for the two primary outcomes and mortality/NDI is considered as a secondary outcome then the table below gives the total sample size required for a 5% overall level test at 80% and 90% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and a conservative outcome rate of 50% in making the calculations. These sample sizes are given in the N1 column and would also allow a 10% difference in NDI/death to be detected with a power of 73%. If an 80% power is desired for the NDI/mortality outcome this would result in sample sizes in the N2 column.

TOTAL SAMPLE SIZES REQUIRED

	80% Power		90% Power	
Detectable Difference (absolute %)	Total N1*	Total N2**	Total N1*	Total N2**
8%	1792	2096	2284	2676
9%	1388	1624	1792	2096
10% (multiples to same arm)	1120	1312	1456	1704
11%	940	1104	1208	1416
12%	784	920	1032	1208
13%	672	788	860	1008
14%	584	680	756	880
15%	504	588	652	768

* sample sizes to insure the appropriate power for the two primary outcomes (BPD/Death, ROP/Death)

** sample sizes to insure the appropriate power for the secondary outcome (NDI/Death)

We have increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduces a clustering effect into the design. The analysis of the GDB data base resulted in the 1.12 estimate. We also inflated the sample sizes by 17% to adjust for attrition after discharge and before follow-up. This figure was also determined from the GDB data base. Thus the actual sample size for this trial would be 1310 for 80% power for detecting an absolute difference of 10% in the two primary outcomes and the NDI secondary outcome. This sample size is not sufficient to permit detection of interactive effects between the two treatments with reasonable power.

HYPOTHESIZED TREATMENT EFFECTS FOR SUPPORT

When sample sizes were estimated for the SUPPORT trial the following base rates for the three outcomes (rounded) were calculated from the GDB:

--BPD/Mortality—67%
--ROP $\geq$ Grade III/Mortality—47%
--NDI/Mortality—61%.

Sample sizes were calculated for a range of absolute treatment effects and 10% seemed to be the smallest plausible effect for the study. Rounding the above rates to 65, 45, and 60 percent the following tables show what the data would look like under the assumption of a 10% reduction in outcome and control rates of 65, 45, and 60 percent for the DRCPAP (No)/ SpO2 (High) group. Interactive effects are assumed to be zero. Tables are presented which show treatment effects when both treatments affect the BPD and the ROP outcomes and when only one of the treatments affects outcome. The NDI table is only for the case where both treatments affect outcome.

Table IA

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on BPD/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO2

CPAP	Low	High	Overall
Yes	45	55	50
No	55	65	60
Overall	50	60	55

Table IB

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on BPD/Mortality **Assuming a 10% Main Effect for CPAP Only**—Table Entries are Outcome Rates (%)

SpO2

CPAP	Low	High	Overall
Yes	55	55	55
No	65	65	65
Overall	60	60	60

Table IIA

Treatment Effects for SpO2 (High, Low) and DRCPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO2

SpO2

CPAP	Low	High	Overall
Yes	25	35	30
No	35	45	40
Overall	30	40	35

Table IIB

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for SpO2 Only**—Table Entries are Outcome Rates (%)

		SpO2		
		Low	High	Overall
CPAP	Yes	35	45	40
	No	35	45	40
	Overall	35	45	40

Table III

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on NDI/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

		SpO2		
		Low	High	Overall
CPAP	Yes	40	50	45
	No	50	60	55
	Overall	45	55	50

9.1 Quality Control

The selection of personnel will be left to the site PI's. No specific job descriptions are required for this protocol. The actual duties of the individual who will perform the randomization will be detailed in the manual for the study. Protocol violations will be reviewed, and if frequent, may require a site visit and consideration for termination of a collaborating site.

10.1 Risks and Benefits

Potential risks to the use of CPAP and/or PEEP include pneumothoraces; however this is unlikely to be increased over the risk of PPV alone. The level of CPAP/PEEP will be set at 5-6 cmH_2O, a level that is not thought to increase the incidence of pneumothorax. Recent data from Dr Morley suggest that this level is probably the lowest effective level especially when the infant's mouth is open, and is well tolerated. Objections to use of PEEP or CPAP could be countered by the argument that the majority of neonatologists use PEEP in resuscitation, thus the standard of care at most centers probably include the administration of CPAP and/or PEEP. Another potential risk is the administration of CPAP in the DR to infants without respiratory distress, which could conceivably cause vagal stimulation and resultant bradycardia and gastric distension.

Perhaps the major risk of this trial is that the known benefit of early surfactant with a reduction of death and disease severity, and a reduction of BPD with natural surfactant may not be offset by the early use of CPAP. However, the increasing trend in the use of early CPAP without such evidence represents an even greater risk.

Appendix A

Study Tables

Table 1. Patient Description

	Treatment	Control	P Value
Birth weight (grams) (M + SD)			
Gestation (weeks) (M + SD)			
Apgar 1 min < 3 Assigned			
Apgar 5 min < 3 Assigned			
Received PPV (Number, %)			
Surfactant in DR (Number, %)			
Received Chest Compression (N%)			
Received Epinephrine (N, %)			

Table 2. Other Outcomes

	Treatment	Control	P Value
Total Duration of Mechanical Vent (M +SD)			
Duration of Oxygen (Total days)			
Duration of CPAP			
Duration of nSIMV			
% alive off MV by Day 7 (+SD)			
Pneumothoraces (N, %)			
Other air leaks (N, %)			
BPD at 36 weeks (O_2 dependence)			
BPD by Physiologic Definition (N%+SD)			
Survived to discharge (N,% +SD)			
Number Never Intubated (N, %)			
Number receiving PNS for BPD (N, % %)			
Alive without neurdevelopmental impairment at (18-22 months) years (N, %, +/-SD)			

Appendix B

Study Tables

Table 1. Patient Description

	Low Saturation	High Saturation	RR	CI	p value
Birth weight (grams) (M + SD)					
Gestation (weeks) (M + SD)					
Race (W, B, H, other) %					
Antenatal steroids (%)					
Apgars ≤3 at 5 min					

Table 2. Primary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Threshold ROP/Surgery or death by 36 weeks (%)					
Death by 36 weeks (%)					
Threshold ROP in alive infants at 36 weeks (%)					
BPD or Death by 36 weeks (%) ±					

Table 3. Secondary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Death by discharge status (%)					
BPD in alive infants at 36 weeks (%)					
IVH 3 or 4/PVL or death by 36 weeks (%)					
IVH 3 or 4 in alive infants at 36 weeks (%)†					
Cystic PVL in alive infants at 36 weeks (%)†					
Neurodevelopmental impairment or death by 18-22 months (%)					
Death by 18-22 months (%)					
Neurodevelopmental impairment at 18-22 months (%)†					
Cerebral palsy at 18-22 months (%)†					
MDI < 70 (%)					
PDI < 70 (%)					
Any blindness at 18-22 months (%)†					
Unilateral blindness at 18-22 months (%)†					
Deafness at 18-22 months†					

†Analyzed for survivors

Table 4. Other Outcomes

	Low Saturation	High Saturation	RR CI	P Value
Total Duration of Ventilation (M+SD)				
On ventilator or death by day 7 (%)				
Pneumothorax (%)				
Any air leak (%)				
Postnatal steroids for BPD (%)				
Necrotizing enterocolitis ≥2 (%)				
PDA requiring surgery				

	Early CPAP/Early Extubation	Prophylactic Surfactant
Delivery Room Management	Resuscitate using CPAP. If necessary, initial PPV settings PIP 15-25, PEEP 5. Transport on CPAP If intubated for resuscitation, give surfactant within 1 hour of age. Do not intubate unless indicated by NRP guidelines	Intubate and give surfactant within 1 hour of age Transport with PPV according to SOC
Upon NICU Admission	Randomize within 2 hours to Pulse Oximeter	Randomize within 2 hours to Pulse Oximeter
Intubation Criteria	**Not Required. May intubate for ANY of these criteria** • FiO_2 >.50 required to maintain indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour • $PaCO_2$ > 65 torr (art. or cap. samples, if venous $PaCO_2$ > 70 torr) documented on a single blood gas • Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. **If intubated, give surfactant within the first 48 hrs if in respiratory distress**	**Reintubation Criteria** **Standard of Care**
Extubation Criteria	**Attempt extubation within 24 hours of fulfilling all of the following criteria:** • $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples) • An indicated SpO2 $\geq$ 88% with an FiO2 $\leq$ 50% • Mean airway pressure (MAP) < 10 cm H_2O, vent rate $\leq$ 20 bpm, amplitude < 2X MAP if on HFV • Absence of clinically significant PDA • Hemodynamically stable	**Keep intubated and ventilated until criteria met. Attempt extubation within 24 hours of fulfilling all of the following criteria** • $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples) • FiO2 $\leq$ 35 with SpO2 > 88% • Mean airway pressure (MAP) < 8 cm H_2O, vent. rate $\leq$ 20 bpm, amplitude < 2X MAP on HFV • Absence of clinically significant PDA • Hemodynamically stable
Repeated Surf Doses	Subsequent doses may be given at the manufacturer's recommended dose up to a total of 4 doses.	
Intubation	Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery	
CPAP D/C	In room air for at least 1 hour	
CPAP Resumption	At any time	
Duration of Intervention	14 days	14 days

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DATE: February 2, 2005

TO: Dr. Joseph Bellanti

FROM: Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NICHD, NIH

RE: SUPPORT Trial Follow-on Study of Outpatient Pulmonary Outcomes

Enclosed you will find a copy of the protocol "**SUPPORT Trial Follow-on Study of Outpatient Pulmonary Outcomes**" which the Neonatal Research Network Steering Committee has recently approved. I have asked you, as one of a group of investigators with special expertise, to review the protocol for the Network. Please consider the following questions for comment in your review, which will be anonymous upon request.

1. Is the question significant? Is the question still unresolved?

2. What are the strengths and weaknesses of the following design elements:
   a. Primary and secondary outcome measures
   b. Eligibility, inclusion and exclusion criteria
   c. Study groups
   d. Assignment
   e. Masking
   f. Surveillance for complications
   g. Follow-up

3. Are there other important ancillary protocols (to be done at individual centers)? Should any ancillary project be a part of the primary study?
4. Do you anticipate any other problems with the protocol?
5. Please comment on the feasibility of the study.

Please feel free to comment on any other issues you feel are relevant.

Thank you for agreeing to review this protocol. The addition of external review to the process of protocol development of our trials has been invaluable.

Please email or fax your written response to me at higginsr@mail.nih.gov or (301) 496-3790 by March 1, 2005. Feel free to call me directly with any questions at (301) 435 - 7909
\protorev\extrev.wpd

From: Higgins, Rosemary (NIH/NICHD)
To: Willson, Douglas F *HS
Subject: RE: NICHD Neonatal research Network Confidential Protocol Review
Date: Wednesday, February 02, 2005 4:08:00 PM
Attachments: Willson Feb 2, 2005.doc
SUPPORT Follow-on Study 10-1 (2).doc
Appendix A.doc
Appendix B.doc
Appendix C.doc

Doug
Thanks in advance. Attached is the secondary protocol for pulmonary outcomes and the main trial SUPPORT Protocol. There is a list of instructions. Call me if you have any questions.
Rose

-----Original Message-----
From: Willson, Douglas F *HS [mailto:DFW4M@hscmail.mcc.virginia.edu]
Sent: Monday, January 31, 2005 5:52 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: NICHD Neonatal research Network Confidential Protocol Review

Rose,
For you, anything! If need be could I run it by a colleague of mine in Pulmonary who may be more expert?

Doug

Douglas F. Willson, MD
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> From: Higgins, Rosemary (NIH/NICHD)
> Sent: Monday, January 31, 2005 4:33 PM
> To: dfw4m@Virginia.EDU
> Subject: NICHD Neonatal research Network Confidential Protocol Review
>
> Hi Doug,
>
> Based on your expertise, I am wondering if you could confidentially review a protocol for the NICHD Neonatal Research Network titled NICHD SUPPORT Trial Follow-on Study of Outpatient Pulmonary Outcomes? This is a secondary study to a main trial to look at pulmonary outcomes in very low birth weight infants. Let me know if you could complete a review by February 28 and I can send you instructions and the protocol.
>
> Thanks in advance!
>
> Rose
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> Rosemary D. Higgins, M.D.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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DATE: February 2, 2005

TO: Dr. Douglas Willson

FROM: Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NICHD, NIH

RE: SUPPORT Trial Follow-on Study of Outpatient Pulmonary Outcomes

Enclosed you will find a copy of the protocol "**SUPPORT Trial Follow-on Study of Outpatient Pulmonary Outcomes**" which the Neonatal Research Network Steering Committee has recently approved. I have asked you, as one of a group of investigators with special expertise, to review the protocol for the Network. Please consider the following questions for comment in your review, which will be anonymous upon request.

1. Is the question significant? Is the question still unresolved?

2. What are the strengths and weaknesses of the following design elements:
   a. Primary and secondary outcome measures
   b. Eligibility, inclusion and exclusion criteria
   c. Study groups
   d. Assignment
   e. Masking
   f. Surveillance for complications
   g. Follow-up

3. Are there other important ancillary protocols (to be done at individual centers)? Should any ancillary project be a part of the primary study?
4. Do you anticipate any other problems with the protocol?
5. Please comment on the feasibility of the study.

Please feel free to comment on any other issues you feel are relevant.

Thank you for agreeing to review this protocol. The addition of external review to the process of protocol development of our trials has been invaluable.

Please email or fax your written response to me at higginsr@mail.nih.gov or (301) 496-3790 by March 1, 2005. Feel free to call me directly with any questions at (301) 435 - 7909
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NICHD SUPPORT Trial Follow-on Study of Outpatient Pulmonary Outcomes

University of Rochester
Golisano Children's Hospital at Strong

Timothy P. Stevens, MD
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Dale Phelps, MD

Proposal Updated: October 1, 2004

Contact Information:

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A. ABSTRACT

Statement of Problem Premature infants have a greater risk for wheezing and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor for later wheezing, the etiology of recurrent wheezing in formerly premature infants is not known.

Hypotheses The goal of the clinical project detailed here is to understand better the antecedents of recurrent wheezing among preterm infants during early childhood by evaluating the effect of treatment with different levels of targeted oxygen saturation in the immediate neonatal period. **The overarching hypothesis is that premature infants exposed to supplemental oxygen suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater symptomatic airway dysfunction when challenged with subsequent environmental or infectious exposures.**

Hypothesis #1- Relative to infants managed with a higher SpO2 range, infants who are managed with a lower targeted SpO2 range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' corrected age (CA) whether they develop CLD or not.

Hypothesis #2- Relative to infants managed with prophylactic surfactant and conventional ventilation, infants who are managed with the early use of CPAP and a permissive ventilator strategy will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' CA whether they develop CLD or not.

Design

Longitudinal follow-up of infants enrolled in the SUPPORT Trial to determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the prevalence of recurrent wheezing and volume of outpatient pulmonary care in the first 18 months' CA.

Definition of outcomes:

A) Parental Report of Wheezing
B) Physician Diagnosed Wheezing.
C) Volume of Outpatient Pulmonary Care including number of pulmonary medications, office and emergency room visits and re-hospitalizations for respiratory illnesses.

Ascertainment of outcomes:

Outcomes will be measured at 4 time points in the first 18-22 months' CA as follows:

1. NICU discharge -baseline interview at to obtain family and environmental history
2. Six months' CA - telephone interview to ascertain prevalence of wheezing and obtain interval history of need for pulmonary care.
3. Twelve months' CA - telephone interview as at 6 months'
4. 18-22 months' CA- Prior to NICHD follow-up clinic visit, a telephone interview to ascertain prevalence of wheezing and obtain interval history of need for pulmonary care will be administered and primary care physician contact information collected for outpatient office chart review.
5. Outpatient chart review- data extraction from patient outpatient medical record.

Anticipated Results

We anticipate that, for infants who develop CLD and those who do not, treatment with a lower vs. higher targeted oxygen saturation range will result in less frequent episodes of wheezing and less need for outpatient pulmonary care in the first 18-22 months' CA.

Benefits and Risks

The proposed SUPPORT Follow-on Pulmonary Outcome Study will directly measure symptomatic airway dysfunction and outpatient pulmonary morbidity in infants treated with either a higher vs. lower targeted oxygen saturation. These data will provide important insight into the effect of different levels of supplemental oxygen exposure on airway growth and development in formerly premature infants. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the neurodevelopmental follow up visit. We anticipate no risk to the patient of this observational follow-on study.

B. STATEMENT OF THE PROBLEM

Premature infants have a greater risk for wheezing and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor for later symptomatic airway dysfunction, the etiology of recurrent wheezing in formerly premature infants is not known.

C. HYPOTHESES

The overarching hypothesis is that premature infants exposed to supplemental oxygen and, to a lesser extent, mechanical ventilation, in the neonatal period suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction and respiratory symptoms when challenged with subsequent environmental or infectious exposures.

Specific Hypotheses:

Hypothesis #1- We hypothesize that relative to infants managed with a higher SpO2 range, infants managed with a lower SpO2 range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care at 18-22 months' CA.

Hypothesis #2- We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

Hypothesis #3- We hypothesize that **among infants with CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

Hypothesis #4- We hypothesize that **among infants without CLD**, infants managed with early use of CPAP and permissive ventilator strategy relative to infants managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

D. SPECIFIC AIMS

The goal of this project is to understand better the etiology of recurrent wheezing among formerly premature infants during early childhood by examining the interaction of oxygen exposure (targeted SpO2 range), surfactant therapy and early nasal CPAP in the newborn period.

SA#1 - Measure the effect of lower vs. higher targeted SpO2 on the prevalence of recurrent wheezing and volume of outpatient pulmonary care among infants born $24^{0/7}$ - $27^{6/7}$ weeks' gestation during the first 18-22 months' CA.

SA#2 - Measure the effect of early CPAP and permissive ventilator strategy compared with prophylactic surfactant and traditional ventilator strategy on the prevalence of recurrent wheezing and volume of outpatient pulmonary care among infants born 24-27 weeks' gestation during the first 18-22 months' CA.

SA#3 – Among infants who develop CLD, determine whether CLD is milder in infants managed with low compared with high targeted SpO2 by measuring recurrent wheezing and volume of outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

SA#4 – Among infants who do not develop CLD, determine whether pulmonary outcome is better for infants managed with a low compared with high targeted SpO2 range by measuring the prevalence of recurrent wheezing and need for outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory

strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

E. RATIONALE/JUSTIFICATION

Although synergy in producing airway injury may exist between oxygen toxicity and mechanical forces applied to the lung, animal and human data suggest that exposure to high concentrations of supplemental oxygen alone is sufficient to cause airway narrowing and greater reactivity to subsequent challenges. Understanding the relative contributions of oxygen toxicity and mechanical forces on airway growth and development may facilitate development of targeted therapies for preventing or reducing symptomatic airway dysfunction in premature infants.

Why measure recurrent wheezing and outpatient pulmonary care as an outcome from a clinical NICU interventional trial?

1) Important information will be available on the effect of oxidant gas exposure on airway development and later symptomatic airway dysfunction. Exposure to oxidant gas has been causally linked with later wheezing. Existing data on the relationship between supplemental oxygen therapy and wheezing come from longitudinal cohort studies, a design that suffers from intrinsic limitations that make controlling for potential confounders of respiratory outcome difficult. By randomizing infants to higher vs. lower target saturation ranges, and thereby presumably higher or lower concentrations of inspired oxygen, *the SUPPORT Trial creates a unique, and perhaps the only, opportunity to evaluate the effect of different levels of supplemental oxygen on subsequent symptomatic airway dysfunction and need for outpatient pulmonary care after NICU discharge.*

2) Using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care can be directly quantified, allowing assessment of whether infants both with and without CLD have improved pulmonary health as a result of the study intervention.

3) The incidence of CLD, defined as an oxygen requirement at 36 weeks' PMA, is an incomplete measure of pulmonary outcome in formerly premature infants during early infancy. CLD as defined above reflects alveolar gas diffusion and NICU oxygen needs. However, outpatient pulmonary morbidity for formerly premature infants is often airway related, involving wheezing either as a primary symptom such as bronchiolitis or as a complicating symptom of lower respiratory tract infection such as pneumonia. The studies proposed here will directly measure the effect of a randomized NICU-based clinical intervention on symptomatic airway dysfunction and outpatient pulmonary morbidity.

4) The risk of a negative trial is reduced. Because the diagnosis of CLD does not completely predict need for outpatient pulmonary care, clinically significant improvements in pulmonary morbidity may occur with minimal or no change in the incidence of CLD. This result has occurred in other interventional trials in which no difference in CLD were observed (12).

5) At present, there is no standard way to measure symptomatic airway dysfunction in premature infants in NICHD pulmonary intervention trials. There is need for a better measure to assess clinical pulmonary outcome to recognize and promote therapies that reduce need for outpatient care of former extremely premature infants.

6) By measuring outpatient pulmonary outcomes, the cost-effectiveness of the SUPPORT study interventions can be assessed. It is reasonable to expect that the SUPPORT Trial interventions will improve outpatient pulmonary outcomes for infants who ultimately develop CLD as well as those who do not. This proposed follow-on study collects the primary data necessary to quantify the cost-effectiveness of this therapy.

F. BACKGROUND / PREVIOUS STUDIES

Recurrent Wheezing In Preterm Infants is a Significant Public Health Problem

Outpatient pulmonary morbidity, especially recurrent wheezing and need for outpatient pulmonary care, is an understudied but clinically important outcome measure for former premature infants with and without CLD. Infants born weighing < 1500 grams (very low birth weight, VLBW) and especially infants born weighing < 1000 grams are at increased risk for small airway narrowing, airway hyperreactivity, wheezing, and nighttime cough (1-11). Up to 30-40% of formerly extremely premature infants have episodes of wheezing after NICU discharge with many requiring bronchodilators and frequent health care visits. Up to 40-50% of premature infants require re-hospitalization, mostly for treatment of respiratory illnesses (9;12;13). In analysis of cross sectional data from the National Maternal Infant Health Survey and 1991 Longitudinal Follow up Survey, the prevalence of asthma-like recurrent wheezing varied markedly with birth weight. Infants with normal birth weight (NBW, > 2500 grams) had a 6.7% prevalence of asthma compared to 10.9% of low birth weight infants (LBW, 1500-2499 grams) and 21.9% for VLBW (14). Mean per capital asthma related costs have been estimated to be 5 times greater for VLBW compared with NBW infants. The net effect is that VLBW infants, who comprise 2% of asthma patients, consume up to 7% of asthma-related therapy costs (14).

Animal Studies

Animal studies suggest that exposure of the premature lung to hyperoxia (without concomitant mechanical ventilation) for relatively brief periods is sufficient to cause airway remodeling and smooth muscle changes that predispose toward airway narrowing and hyperreactivity to subsequent environmental challenges (15-18). In a rhesus monkey model of asthma, Schlegle et al. exposed infant monkeys to repeated cycles of inhaled House Dust Mite Allergen (HDMA), ozone or filtered air. While repeated exposure to either ozone or HDMA had mild effects, exposure to cycles of ozone followed by HDMA resulted in asthma like changes with significant increases in serum IgE, serum histamine, peripheral eosinophilia and greater airway reactivity. Using supplemental oxygen rather than the stronger oxidant ozone, Schulman et al. found that exposure of newborn guinea pigs to 70% oxygen for 96 hours resulted in airway hyperreactivity at 2 and 9 days after the cessation of oxygen. In cell models, intracellular glutathione buffers airway cells against oxidant injury during hyperoxia (19;20). Although the critical period for lung development is comparatively brief in laboratory animals compared with human infants, the duration of hyperoxic exposure (and risk of oxygen toxicity) for treatment of neonatal lung disease may extend for much longer periods in premature infants known to be deficient in anti-oxidant systems such as intracellular glutathione.

Premature Infants <u>With CLD</u> Are At Greatest Risk For Recurrent Wheezing

Among premature infants, infants with bronchopulmonary dysplasia (BPD) are at highest risk for poor pulmonary outcome after NICU discharge. Infants with CLD have small airway compromise with decreased forced expiratory flow velocities, airway hyperreactivity, and increased functional residual volume suggesting airway obstruction (2;5;9;21-24). In a pulmonary follow up of infants with HMD or BPD, De Klein et al. found infants with BPD had reduced FEV1 at baseline while infants with RDS but not BPD had significant improvements in FEV1 following bronchodilator therapy. In this study, a history of recurrent wheezing predicted abnormal pulmonary function (25). In a recent study of infants with CLD, Robin et al. found that 50% of infants with CLD had symptoms of recurrent wheezing and 35% showed significant airway responsiveness to bronchodilators, evidenced by a 24% increase in forced expiratory flow velocity at 75% of expired forced vital capacity (FEF_{75}). This study demonstrated the relationship between recurrent wheezing as a clinical symptom and the physiologic measurement of airway obstruction. Infants with CLD and a history of recurrent wheezing showed greater expiratory flow limitation, hyperinflation, and airway responsiveness to albuterol compared to those without a history of recurrent wheezing (24).

Premature Infants Without CLD Have Significant Airway Dysfunction

Among VLBW infants who do not develop CLD, several studies of pulmonary outcome have found an association between neonatal oxygen exposure and increased prevalence of expiratory flow dysfunction and airway hyperreactivity (4;11;26-29). Some authors attribute reductions in airway function to intrinsically small airways as a consequence of poor intrauterine growth rather than superimposed airway injury or reactivity from neonatal respiratory disease (1;30). However, because small airways alone do not fully explain findings of airway hyperreactivity, other mechanisms of small airway dysfunction are necessary to explain respiratory symptoms.

Several pulmonary outcome studies have reported significant increases (2-fold or more) in airway obstruction among VLBW infants without CLD following exposure to as little as an FIO2 of 0.4 for 5 days (3;4;8;26). Not all studies have had similar results suggesting variability in effect or susceptibility of babies to oxygen exposure (31;32). In 1982, Coates et al. described increased small airway resistance at 10 year follow up of mildly premature infants (mean gestational age 31 weeks and birth weight 2000 grams) treated with a high oxygen (O2) regimen and those exposed to a low O2 regimen for the treatment of respiratory distress syndrome (RDS). Mechanical ventilation was not used in either group. Pulmonary function tests were performed on survivors receiving either the low or high supplemental oxygen regimen ten years after their initial illness. Infants treated with high levels of supplemental oxygen alone (no mechanical ventilation) had decrements in airway function similar to decrements in function reported for a historical cohort of RDS survivors treated with ventilation and high levels of supplemental oxygen. From these data, the authors concluded that neonatal exposure to high oxygen concentrations in the absence of mechanical ventilation is capable of causing long-term change in small airways (28). These studies suggest that use of lower supplemental oxygen concentration may improve respiratory health of infants who do not develop CLD.

Premature Infants Without CLD Have Increased Risk of Recurrent Wheezing and Need for Outpatient Pulmonary Care.

For VLBW infants without CLD, the prevalence of parental or physician reported wheezing is increased compared with term infants, with estimates of the prevalence of wheezing ranging from 10-38% (4;8). Prevalence of wheezing requiring medications is greater compared with term infants. VLBW infants have a 2-4-fold increase in respiratory related re-hospitalization rates compared with term infants (4;8;33-35). Although most studies have found the risk of recurrent wheezing remains elevated throughout childhood, an Australian longitudinal follow-up cohort of VLBW infants found the prevalence of wheezing remained elevated for 2 years then returned to baseline (32;36).

Prevalence of Symptomatic Airway Dysfunction in Formerly Preterm Infants During the Surfactant Era Remains High

With the advent of surfactant therapy, survival for small infants increased dramatically and the incidence of CLD changed minimally (37-40). Classic BPD evolved into the new CLD characterized by reduced alveolarization and more variable airway changes (41). Pulmonary follow up studies during the surfactant era showed reduced pulmonary morbidity in surfactant treated patients. Typical of these studies, Sell et al. found the incidence of asthma was significantly lower in infants given synthetic surfactant compared with those given air placebo. Pelkonen et al. performed PFT measurements on 40 children aged 7-12 years who were born before 30 weeks of gestation with an immature surfactant system, and were randomized to one of three treatment groups: prophylactic surfactant, rescue surfactant and placebo (air). Spirometric parameters of preterm born children were compared with those of 20 children born at term. Bronchial obstruction was found in 53% of the prophylactically treated group, in 36% of the rescue group, in 67% of the placebo group, and in 0% of the control group (42). A recent report suggests that the introduction of surfactant therapy markedly altered the pulmonary outcome of premature infants. Published in 2001, the Newborn Lung Function Project Group reported results of a prospective 12-year follow-up of VLBW infants following the introduction of surfactant therapy. Among infants with CLD, wheezing symptoms decreased from 50 to 16% from the period before compared with the period after surfactant therapy became available. However, among infants without CLD the prevalence of wheezing increased from 14% to 38% with the introduction of surfactant. These data suggest that surfactant therapy has an effect on outpatient respiratory health and underscores the need to

consider outpatient pulmonary outcomes in evaluating therapeutic strategies that potentially decrease surfactant replacement therapy.

CLD is an Incomplete Predictor of Outpatient Pulmonary Morbidity

Several authors have looked to respiratory symptoms and need for outpatient pulmonary care as outcome measures for neonatal lung disease (9;10;12;24). In 1988, from a retrospective chart review of 605 premature infants < 1500 grams, Shennan et al. found that the presence of BPD (oxygen requirement at 36 weeks PMA) had a 63% positive predictive value and a 90% negative predictive value for abnormal pulmonary outcome in the first 2 years of age. However, this study from before the era of exogenous surfactant therapy defined abnormal pulmonary outcome as death, oxygen requirement at 40 weeks PMA, 2 or more respiratory related hospital admissions, wheezing requiring drug therapy or persistent wheezing resulting in growth failure, handicap or hypotonia at 1 year of age. Such restrictive criteria for abnormal pulmonary outcome are likely to underestimate the burden of recurrent wheezing on former premature infants and their families. Several recent interventional studies show that CLD is an incomplete predictor of clinical wheezing and need for outpatient pulmonary care and suggest that differences in oxygen exposure or oxidant stress may affect pulmonary outcome without affecting the incidence of CLD.

Interventional Trials That Did Not Reduce CLD But Did Reduce Outpatient Pulmonary Morbidity.

Recent data in preterm infants treated with human recombinant superoxide dismutase (SOD) found that anti-oxidant therapy did not reduce the incidence of CLD. However, among infants < 27 weeks gestation SOD therapy resulted in significant reductions in the first year after NICU discharge in the number of emergency room visits and number of re-hospitalizations for respiratory problems and reductions in the need for bronchodilators suggesting a reduced prevalence of wheezing in patients treated with SOD (12). In a randomized, multi-center trial from Helsinki, N acetyl cysteine did not reduce the incidence of CLD. Outpatient pulmonary outcome of these patients has not been reported.

Treatment of Premature Infants With Higher Targeted Oxygen Saturations Is Associated with Poorer Pulmonary Outcome

In the STOP-ROP Study, infants exposed to higher levels of oxygen to achieve a targeted saturation of 96-99% compared with 89-94% had greater risk of adverse pulmonary events including pneumonia, chronic lung disease exacerbations and need for diuretics, oxygen and hospitalization at 3 months'' corrected age. *Although all infants in this study had CLD at enrollment, different targeted oxygen saturation were associated with large differences in pulmonary morbidity.* Adverse pulmonary outcomes occurred with differences in FIO2 of as little as 10% for patients treated with ventilation, CPAP or hood (36% $\pm$ 14% vs. 46% $\pm$ 20%, respectively for low vs. high saturation range) and 5% for infants treated with nasal cannula, (26% $\pm$ 6% vs. 31% $\pm$ 11%, respectively for low vs. high saturation range) (44). In a similar study, The Benefits of Oxygen Saturation Targeting (BOOST) Trial randomized infants < 30 weeks' gestation to higher (95-98%) or lower (91-94%) saturations ranges beginning at 32 weeks' PMA to determine whether infants managed with higher targeted saturation range showed better growth and neurodevelopment. As in the STOP-ROP study, need for oxygen therapy was prolonged. Trends towards an increased risk of pulmonary death and fewer outpatient office visits (median 27.5 vs. 31.3, $p < .11$) were seen in the lower targeted oxygen saturation group (13).

G. METHOD/ PROCEDURES

NICHD SUPPORT Trial Follow-on Study of Pulmonary Outcomes

G.1 Description of study design

This study will add an 18-22 month longitudinal, prospective follow-on study of surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial.

G.2 Definition of study population

Infants with gestational age of $24^{0/7}$-$27^{6/7}$ weeks' gestation by best obstetrical estimate.

Inclusion criteria:

- Full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Parents/legal guardians have provided consent for enrollment
- No known major congenital malformations
- Survival to hospital discharge

Exclusion Criteria

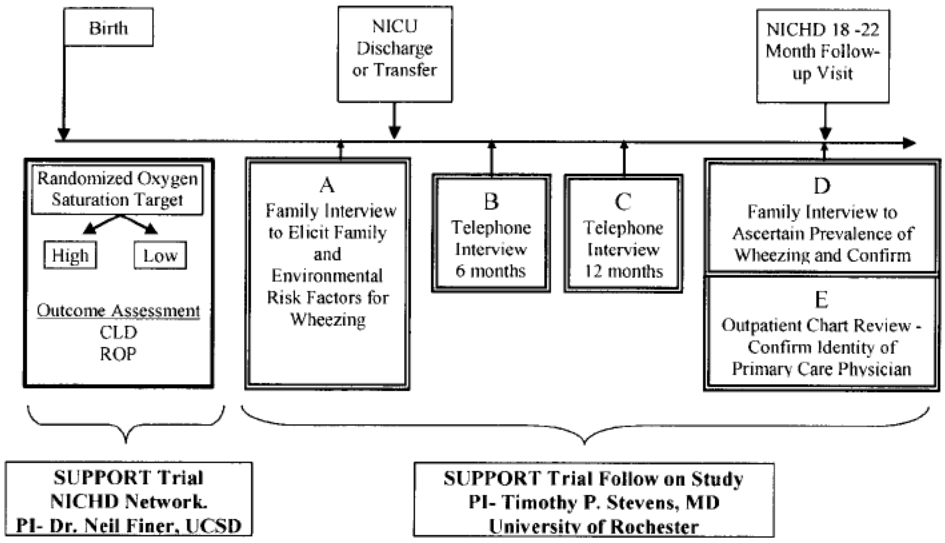
- Transport to the center after delivery
- Parents/legal guardians refuse consent
- Research apparatus/study personnel are not available.
- Gestational age $< 24^{0/7}$ or $\geq 28^{0/7}$ weeks' gestation

G.3 Description of study intervention

Before delivery, infants will be randomized to subsequent management with high vs. low target oxygen saturation according to the SUPPORT Protocol. The SUPPORT Follow-on Study proposed here begins just prior to NICU discharge (Figure 1).

SUPPORT Trial Follow-on Study

Figure 1. **Infants $24^{0/7}$-$27^{6/7}$ Weeks' Gestation**



"A" will be administered at NICHD Network Centers

"B-E" will be conducted long distance by University of Rochester research staff.

Fig 1, A. Parent (Guardian) Interview to Elicit Family and Environmental Risk Factors for Wheezing The family interview will be administered at each participating Network Center by site study nurses prior to NICU discharge or transfer. The questions are based on intake questions used by the Tucson Respiratory Study and are designed to elicit family history of asthma, atopy, and home environment and to identify likely care givers (Questionnaire in Appendix G). Consent for release of medical information will be obtained to facilitate contacting physician offices to obtain office data.

Fig 1, B. Telephone Interview at 6 months' CA – respiratory interval history

Fig 1, C. Telephone Interview at 12 months' CA – respiratory interval history

Telephone interviews will be undertaken at 6 and 12 months' to obtain limited interval history of respiratory problems including wheezing, medications used, and health services sought for respiratory related problems (Questionnaire in Appendix H).

Fig 1, D. Parental Interview to Ascertain Prevalence of Wheezing and Confirm Risk Factors This parent interview will also be administered by telephone, prior to the regularly scheduled 18-22 month NICHD developmental follow up clinic visit (an NICHD funded, ongoing program). Contacting parents prior to the office visit will help improve the Developmental Follow Up Clinic attendance rate and will allow the clinic visit to provide a back up means to contact the family. All telephone interviews, the 2 limited telephone interviews and the second family history interview at 18-22 months', will be conducted long distance from Rochester (see below). The interview questionnaires are based on questionnaires administered by the Tucson Respiratory Study at approximately one year of age (Questionnaire in Appendix I). Questions are designed to ascertain the frequency and severity of wheezing episodes. In addition, risk factors obtained at the 1st interview will be confirmed or updated.

Fig 1, E. Outpatient Chart Review - Confirm Identity of Primary Care Physician

To confirm results of physician report of wheezing obtained by telephone interview, patients undergoing telephone interview will have their primary care physician's medical record reviewed.

E.1 – Physician report of wheezing

E.2 – Frequency of outpatient pulmonary care. The volume of outpatient pulmonary care including outpatient primary care physician office visits, pulmonary specialty care, emergency room visits, hospitalizations and the number and duration of pulmonary medications will be obtained from primary care physician chart review. To help assure compliance by primary care office staff, a $25 honorarium will be offered for successful completion of the chart review form (45-47).

G.4 Precise definition of primary/secondary outcomes

1) Definition Of Parental Report Of Wheezing. The primary outcome will be parental report of recurrent wheezing, defined as more than 1 episode of wheezing, using questions adapted from the Tucson Children's Respiratory Study, questions validated in a large prospective birth cohort study of term infants (48-54) (Appendices G-I). The primary question used in the telephone interview for this project will be the same as the one used in the Tucson Children's Respiratory Study "Did your child have wheezing?" (48) Additional questions will be used to further characterize the wheezing episodes, identify wheezing associated with a viral illness (parental report of a "cold") and wheezing associated with environmental exposures. The prevalence of health services utilization (outpatient office visits for pulmonary care, ER visits, re-hospitalizations, bronchodilator therapy) for pulmonary reasons will also be collected during interviews. The Tucson study also ascertained frequency of office visits and use of respiratory medications. Of full term infants whose parents reported that their infant had an episode of wheezing, 40% had recurrent wheezing in the first 6 years compared with 22% of infants whose parents reported no episodes of wheezing in the first 3 years.

Parental Report of Wheezing Is A Reliable Outcome Measure of Airway Dysfunction

Evaluation of frequency and severity of respiratory symptoms and volume of pulmonary care has been used as the primary outcome in multiple follow up studies of term and premature infants (10;12;14;43). A recent review evaluated the value of respiratory symptom history ascertained by parental questionnaire in determining the risk for developing asthma in early childhood. By evaluating 9 large, longitudinal, full term birth cohort studies and reviewing the original questionnaire from 7 of these studies, Koopman found that the questions posed to parents

eliciting a history of wheezing in their infants were similar. Parental report of wheezing predicted an increased risk for later respiratory symptoms including asthma. In the studies proposed here, recurrent wheezing ascertained by parental report will be used as the primary outcome, rather than physiologic measurements of airway dysfunction, for several reasons (Table 3). Although the goal of using respiratory questionnaires in the studies proposed here is to measure pulmonary outcome, not to predict asthma, studies of asthma questionnaires and their ability to predict asthma demonstrates the validity of parental report of wheezing as an accurate measure of airway dysfunction.

Reasons to Use Parental Report of Wheezing as Primary Outcome Measure

- Parental interview can be performed more readily on large numbers of patients. The validity of this approach has been shown in several longitudinal studies including The Tucson Respiratory Study, upon which the interview questions are based.
- Recurrent wheezing is highly correlated with changes on pulmonary function testing. In a study of infants with CLD, a history of recurrent wheezing was associated with greater expiratory flow limitation, hyperinflation and airway responsiveness to albuterol on pulmonary function testing compared to those without a history of recurrent wheezing (24).
- Parental recall of respiratory illnesses has been shown to correlate strongly with review of medical office records. For asthma and bronchitis in the past year, Pless et al. found good agreement between recall of 288 parents and physician office chart review. Parental education and occupation were not predictive of a parent's ability to recall the illness (55). In an assessment of parental recall done to evaluate minor injury in children, Harel found recall declined with time, with the best recall occurring in the first 3 months' after injury with further decline after 6 months' from the time of the injury (47;56;57).

Advantages of Conducting Telephone Interviews From a Single Center

Conducting the telephone interviews from Rochester will:

1) require less effort from the individual Network Centers (Network Centers may assist in tracking families)
2) allow standardization of the telephone interview by a core group of trained interviewers
3) blind the telephone interviewer to the SUPPORT Trial study group designation
4) reduce the cost of the study by consolidating the telephone training and follow up at one site.

2) Definition Of Physician Diagnosed Wheezing. A secondary outcome will be physician report of recurrent wheezing, defined as more than 1 episode of wheezing. Physician diagnosed wheezing will be collected by parental report during telephone interviews using the question "Did a doctor tell you your child had wheezing?" and "Where did you see that Doctor, primary care, emergency room, hospital or other?" In addition, review of the primary care physician medical chart will be undertaken to identify episodes of physician documented wheezing.

3) Definitions of Secondary Outcomes - Measures of Volume of Outpatient Pulmonary Care

Important secondary outcomes of outpatient pulmonary morbidity will be collected (Table 1).

Table 1. ***Secondary Outcomes, Covariates and Sources***	
Outcomes	**Source**
Secondary Outcomes	
Number and duration of outpatient pulmonary medications including bronchodilator, diuretic, methylxanthine, and inhaled and systemic steroid therapy.	Family interview, primary care chart review
Number of office visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of emergency room visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of re-hospitalizations for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Growth at 18 months' CA (height, weight and head circumference)	NICHD follow up clinic data

Data Collection: Ascertainment of Outcomes - Field Work

Ascertainment of Wheezing and Outpatient Pulmonary Morbidity By Telephone Interview.
There will be 4 parental interviews over 18-22 months', one prior to NICU discharge and 3 subsequent telephone interviews at 6 month intervals to collect data on the prevalence of recurrent wheezing, need for outpatient pulmonary care, and relevant environmental and family history covariates (Figure 1, A-D above). Based on review of longitudinal studies of full term infants in which follow up patient contacts occurred quarterly to once every 18 months', a 6 month interval for follow up patient contacts is planned in an effort to reduce parental recall omissions which are more likely to occur with less frequent follow up (43;56). The 4 interviews are designed to collect the primary and secondary outcomes of the follow-on study. Other inpatient and outpatient data will be collected as part of the NICHD Neonatal Research Network Generic Database (GDB) and Follow-up Program.

The University of Rochester Neonatology Research Group has conducted similar telephone interview designs as part of an ophthalmologic outcome study of patients enrolled in a randomized trial of cryotherapy to treat ROP and a 15-year, longitudinal neurological assessment conducted by telephone survey among 132 infants treated with surfactant. Telephone follow up rates were 96% follow up at 7 years and 95% follow up at 15 years (58). In the study proposed here, the University of Rochester Health Services Research Group (HSR Group), will conduct the telephone interviews.

In telephone follow up surveys conducted by the HSR Group, follow up rates at 12 months' have exceed 75% in populations at high risk for being lost to follow up (59-65). The Rochester HSR Group has over 2,500 square feet of newly renovated space. Under the direction of Drs. Jonathan Klein and Peter Szilagyi, the HSR group includes sufficient space and all appropriate equipment and personnel to perform telephone interviews and database management for the project presented here. The HSR Group will conduct 3 telephone interviews from Rochester. Drs. Peter Szilagyi and Jonathan Klein, co-directors of the HSR Group, are mentors for Dr. Stevens' K23 Patient Oriented Research Award application. Drs. Klein and Szilagyi will work with Dr. Stevens and Dr. Phelps in the implementation and management of the tracking and respiratory questionnaire program. To facilitate tracking and record keeping, Dr. Stevens will design and write a database to track enrolled patients and their contact information, next scheduled interview, and record answers to phone interview questions. Each interview will close with a question as to whether the family plans a new address or phone number prior to the next interview. The names and phone number of a friend or relative and their primary care physician will be sought so that they may be contacted in the event that contact with the patient is lost. By interviewing families every 6 months', a higher follow up rate will be achieved because family contact information will not become so out of date that the family is lost or that re-contacting them is inefficient. We anticipate that each interview will require 2 hours of staff time, with 20-30 minutes to conduct the interview and 90 minutes to contact family and enter data.

Interview Instruments – (Appendices A-C) Questionnaires based on the Tucson Children's Respiratory Study, a well validated questionnaire used in a large longitudinal cohort study that followed healthy full term infants from birth to over 20 years of age. The questionnaires have been updated to reflect currently available respiratory medications and modified to address the health issues that are faced by formerly premature infants such as use of palivizumab for RSV prophylaxis. In addition, the questionnaires are designed to elicit a thorough history of possible covariates, such as environmental and infectious exposures and family histories of atopy, asthma or respiratory disease.

Physician Office Records Assessment of Wheezing and Outpatient Pulmonary Morbidity Physician office charts will be reviewed to determine physical findings of wheezing, medication use and respiratory related hospitalization history. For primary care pediatricians, the family's consent authorizing release of medical information and an office contact questionnaire will be mailed or faxed to the provider. The questionnaire will be based on a similar document used by the Rochester Research Group to obtain medical information on respiratory issues. To help assure compliance with completing the questionnaire, a $25 honorarium will be offered to the office staff.

Data Collection: Ascertainment of Environmental and Genetic Covariates

Ascertainment of important environmental exposures and genetic risk factors that might confound the relationship between supplemental oxygen exposure and recurrent wheezing will be obtained along with the primary outcome during the same telephone and family interviews (Table 2). A second follow-on study to the SUPPORT Trial, not affiliated with the studies proposed here, is being independently proposed by other investigators to study specific genetic markers that predict greater risk of CLD. Although synergy between our study and the genetic study potentially exists, the genetic study is not yet funded and may not go forward.

Table 2. Postnatal and Genetic Covariates Evaluated as Potential Confounders of Oxygen and Wheezing

Covariates in Home Environment and Exposures The initial questionnaire and 6 month interviews will gather information on other *inhaled exposures* (tobacco, wood stoves, cold air), *residence* (urban vs. rural residence), *infectious exposures* (RSV, palivizumab) and medical risk factors (gastroesophageal reflux, congenital anatomic airway abnormalities)

Covariates in Family History Questionnaires will elicit *family history* of atopy (family history of asthma, eczema or allergy to foods, pets, molds, pollen or dust).

Data Collection: Ascertainment of Primary Exposure

Oxygen Exposure. In the SUPPORT Trial, it is assumed that managing infants with higher vs. lower targeted oxygen saturation range will result in different levels of supplemental oxygen exposure. Because oxygen is the primary exposure in the SUPPORT Follow-on Study and plays a central role in the disease model proposed, oxygen exposure will be quantified carefully. To document the difference in oxygen exposure between groups, FIO2 values will be recorded and analyzed as described in the SUPPORT Trial.

G.5 Sample size estimate with some statistical support based upon primary outcome

The SUPPORT Trial anticipates enrollment of 1506 patients < 28 weeks' gestation, providing 80% power to detect a 10% difference between treatment groups in the incidence of death/CLD and death/stage III Retinopathy of Prematurity (ROP). Assuming mortality of 35% for infants < 1000 grams (NICHD 2002 data), 978 infants would be expected to survive and be eligible for the SUPPORT follow-on study.

Power for detecting a difference between the high vs. low saturation groups for the primary outcome, recurrent wheezing We expect the prevalence of wheezing to be about 0.17 in the low saturation group, and about 0.31 in the high saturation group(12). For the power calculations, we also consider a scenario with a smaller difference between groups: 0.19 for the low saturation group and 0.29 for the high saturation group. We expect the follow up rate to be about 75%, which would result in data on about 733 patients. We also consider a lower follow up rate of 65%, which would result in about 635 patients. Power to detect a difference between groups based on a chi-square test with type I error alpha set at 0.05 is given in Table 7 for each scenario. From those results, we expect to have more than 80% power for the primary outcome. Also of interest are subgroup analyses, where we look separately at the CLD and non-CLD subjects. Of survivors, we expect 37% or 362 infants to have CLD. For the CLD group, we expect the prevalence of wheezing to be about 0.5 in the high saturation group and 0.3 in the low saturation group. If there is a 75% follow up rate, we will have 92% power to detect a difference between the two groups. For the non-CLD subgroup, we expect the prevalence to be 0.2 and 0.1 in the high and low groups, respectively. With 75% follow up, we will have 85% power. Thus, we expect to have adequate power for the primary outcome even in the analyses stratified by CLD.

Table 3. Power for primary outcome, recurrent wheezing.

Follow up rate	Low Saturation	High Saturation	power
75%	0.17	0.31	0.99
75%	0.19	0.29	0.88
65%	0.17	0.31	0.98
65%	0.19	0.29	0.84

We expect the study to be adequately powered for analysis of important secondary outcomes such as use of pulmonary medications. Based on results reported in Davis et al. for infants less than 27 weeks' gestational age [22], we expect the prevalence rate of pulmonary medications to be 0.42 in the high saturation group, and 0.19 in the lower saturation group. In that case, even with a 65% follow up rate, we would have more than 99% power to detect a difference between the groups with a chi-square test. Similarly, the CLD subgroup analyses would have more than 80% power under those assumptions. Based on the power numbers above, we could potentially enroll fewer subjects in the trial and still have adequate power. However, we choose to over enroll slightly to make up for the fact that some patients will likely be lost to follow up.

Data Analysis.

Analysis of primary dichotomous outcomes will be performed by chi square test and presented as a relative risk for development of that outcome. Number of outpatient pulmonary visits for respiratory illnesses will be presented as median values. The Wilcoxon Rank Sum test, a non-parametric alternative to the two-sample t-test, will be used to test for differences between the two groups. Statistical analyses will need to consider the effect of multiple comparison groups on the level of statistical significance. All analyses will be performed in conjunction with the Research Triangle Institute (RTI, North Carolina), the biostatistical support group for the NICHD Neonatal Network. Data will be presented as shown in tables 4-5. Mean FIO2 values in the high and low SpO2 groups will be compared by two sample t-test. Secondary analyses will be done to evaluate the effect of ventilator strategy on pulmonary outcome and presented similarly to table 4 and 5.

Table 4. ***Primary Dichotomous Outcomes***	**Low Saturation**	**High Saturation**	**RR**	**CI**	**p-value**
Parental Report of Recurrent Wheezing (%)					
Physician Diagnosed Recurrent Wheezing (%)					
Need for Outpatient Pulmonary Medications (%)					
Need for Physician Visit for Respiratory Illness (%)					
Need for Re-hospitalization for Respiratory Illness (%)					

Table 5. ***Primary Outcomes – Continuous Outcomes***	**Low Saturation**	**High Saturation**	**p-value**
Number of Physician Visit for Respiratory Illness (Median)			
Number of Emergency Visits for Respiratory Illness (Median)			
Number of Re-hospitalization for Respiratory Illness (Median)			

Expected Results We predict that premature infants managed with a lower targeted oxygen saturation range compared to those managed with a higher targeted oxygen saturation are exposed to lower levels of supplemental oxygen and have reduced risk of recurrent wheezing in the first 18-22 months' CA.

Anticipated Problems and Solutions

1) Participant attrition. As seen in the sample size calculation, the potential for patients to be lost to follow up over time will be offset by over enrolling patients to participate in the follow up. Because patients who enroll in the SUPPORT Trial are randomized, there should be no systematic bias favoring one group over another among patients who are lost to follow up. However, if loss to follow up is in part caused by the treatment or outcomes, this could bias the results. We will therefore investigate whether there are differences in key variables for subjects who are lost to follow up compared to those who remain in the study. For example, we will test whether subjects in one treatment arm were more likely to be lost to follow up than in the other arm. Similarly, we will compare wheezing rates at 6 months' for those who are later lost to follow up compared to those who remain in the study. We do not expect to see any major differences.
2) Low office respiratory health questionnaire response rate. For primary care offices that do not respond to the first mailing, a repeat questionnaire will be mailed. A phone call to the office will be made if there is no response to the second mailing. A $25 honorarium will also be offered to encourage replies.

3) The SUPPORT Follow-on Study of Pulmonary Outcomes has been prepared as the central project for Dr. Stevens' Patient Oriented Clinical Research Grant (K23 Award), submitted 10/1/04. If approved, funds from the K23 will be available to offset a portion of the cost of conducting this SUPPORT Trial Follow-on study. In the event that the K23 is not funded, I will seek additional funding from alternative sources including The American Lung Association and The March of Dimes Foundation.

G.6 Available population/compatibility with other ongoing protocols

Another secondary study proposed by a group independent from ours is looking at the genetics of reactive airways disease in patients enrolled in the SUPPORT Trial. The follow on study proposed here should be complementary to the genetics study, enhancing the both the quality and quantity of data on the prevalence of wheezing and need for outpatient pulmonary care in patients enrolled in the SUPPORT Trial.

G.7 Estimate of projected recruitment time

The recruitment time will be that of the SUPPORT Trial with a 18-22 month period of follow up to ascertain primary and secondary outcomes.

H. RISKS/BENEFITS, WITH ESTIMATE OF FREQUENCY/SEVERITY OF RISKS.

By using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care may be quantified, allowing assessment of whether infants who develop CLD and those who do not have improved pulmonary health as a result of the study intervention. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the follow up visit. We anticipate no risk to the patient of this observational follow on study.

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SUPPORT FOLLOW-ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED AT TIME OF ENROLLMENT
PRIOR TO NICU DISCHARGE

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

QUESTIONNAIRE: ENROLLED CHILD
(Nurse Administered)

Child's Name: _____ Date: ____/____/____
Mo. Day Yr.

Child's Sex 1. Male 2. Female

Child's Birthdate ____/____/____ Apgar ____/____
Mo. Day Yr.

Person being interviewed:

1. Child's Mother
2. Child's Father
3. Both Parents
4. Child's female guardian
5. Child's male guardian
6. Other woman (SPECIFY RELATIONSHIP) _____
7. Other man (SPECIFY RELATIONSHIP) _____

1. At this time, we would like a little information about the environment in which your new child will grow up. First, how many people live with you in your home?

Total household members: _____

2a. After the first few months, will your child be sharing a room with other family members on a regular basis?

1. Yes
2. No

2b. IF YES: How many people will sleep in the same room with him/her? _____

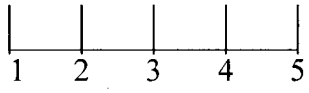
2c. How many living areas are there in your house, excluding closets and bathrooms?_____

3. How many pets are there in the household, either kept inside or out? (RECORD THE NUMBER OF EACH LIVING IN AND OUT OF THE HOUSE).

	Number Kept Inside	Number Kept Outside
Dogs	_____	_____

Cats	_____		_____
Gerbils, Hamsters and Guinea Pigs	_____		_____
Other (Please specify type)			
_____	_____		_____
_____	_____		_____

4. On a scale of 1 to 5, where 1 is not dusty and 5 is very dusty, how dusty would you say your home is compared to other homes in your neighborhood? (CIRCLE APPROPRIATE NUMBER).



Not at all Dusty — Very Dusty

5. Does your home or apartment have air conditioning or some kind of cooling?
   1. Air Conditioning
   2. Evaporative Cooling
   3. Both
   4. None
   5. Other _____
   6. Don't Know

6. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).
   1. Steam or hot water (radiator)
   2. Central gas furnace (furnace)
   3. Electric
   4. Wood Stove
   5. Other
   6. Don't know

7. What fuel is used most for cooking in your home?
   1. Electricity
   2. Gas
   3. Fuel Oil
   4. Wood Stove
   5. Other
   6. Don't Know

8a. Is your child being breast fed? 1. Yes 2. No...SKIP TO QUESTION 9

IF YES,

b. Will this be supplemented with formula? 1. Yes 2. No

c. When do you think the supplement will begin? _____months

d. Do not know when supplements will begin. 1. Yes 2. No

9. Does the mother plan to work outside the home within the next year?
   1. Yes
   2. No
   3. Don't Know

10a. Will your child be cared for by anyone who is not an immediate family member for a major part of the next year?
   1. Yes
   2. No
   3. Maybe

IF YES or MAYBE to 10a:

b. Where will this care be provided?
   1. The parent or guardian's home?
   2. Home of a relative or private sitter?
   3. Day care setting (non-private) ?
   4. Don't Know

c. Will this involve other children, not counting the child's brothers and sisters?
   1. Yes
   2. No

12. Finally, which relative is most likely to have your address in case we lose contact with you?

_____ _____
Name Relationship

_____
Address

_____

SUPPORT FOLLOW ON STUDY

FAMILY HISTORY / FAMILY CONTACT QUESTIONNAIRE - ADMINISTERED PRIOR TO NICU DISCHARGE

1. Name:				
2. Relationship to enrolled child:	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact
3. Age (in years):	________	________	________	________
4. Sex:	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female
5. Does this person currently have:	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
a. Bronchitis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
b. Emphysema?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
c. Bronchiectasis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
d. Asthma?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
e. Inhaled Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
f. Food Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
g. Any other chronic respiratory disease? (SPECIFY)	________ ________	________ ________	________ ________	________ ________
6. How often does this person smoke in the house?	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently

SUPPORT FOLLOW ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED BY TELEPHONE AT 6 AND 12 MONTHS CORRECTED AGE

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Before we begin this interview it would be helpful if you could gather any medications your child has been prescribed or has been taking and have them in front of you. Can you do that now or is there a better time to call you?

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing concerns your child may have.

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

4a. Has his/her chest ever sounded wheezy or whistling?
   3. Yes
   4. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?

1	2	3	4	5
Very rarely				On Most days

e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing ~

g. Has this child's wheezing/whistling occurred as attacks?
   1. Yes
   2. No

h. Has this child ever been awakened at night by wheeze or by shortness of breath?
   1. Yes
   2. No

i. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

j. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES. BE SURE TO COMPLETE QUESTIONS 24 AND 25

5. Does this child's chest sound wheezy or whistling during or shortly after vigorous exercise or crying?
   1. Yes, usually
   2. Yes, occasionally
   3. No

6a. Has he/she ever had episodes of shortness of breath or chest tightness?
   1. Yes
   2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6A:

b. Has this ever occurred when the child is at rest?
   1. Yes
   2. No

c. During the past year, how many episodes did he/she have?

1 2 3 4 5
Few — Very many

d. How old was this child when he/she had the first such episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

OR: check here if the child still has condition: ~

f. Has the child's chest ever sounded wheezy or whistling during episodes of shortness of breath or chest tightness?
   1. Yes
   2. No

g. Has he/she ever seen a doctor for shortness of breath or chest tightness?
   1. Yes
   2. No

h. Has this child ever taken any medicine for shortness of breath?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

7. Has this child ever had a cough when he/she did not have a cold?
   1. Yes
   2. No . . . SKIP TO QUESTION 6

IF **YES** TO QUESTION 5a

b. At what time of the day has this cough usually occurred? (CIRCLE ALL THAT APPLY)
   1.
   1. In the morning, shortly after rising
   2. Later in the day
   3. During the night
   4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?
   1. Yes
   2. No

d. How often has this child been bothered by coughing?

1	2	3	4	5
Very Rarely				On most days

e. How old was the child when he/she first began to cough?
   ____ months

   OR: check here if child is still coughing: _

f. How old was this child when he/she stopped coughing?
   _____ months

g. Has the cough usually been dry or loose?
   1. Dry
   2. Loose

h. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?
   1. Yes
   2. No

i. How often has your child raised phlegm, sputum or mucus when coughing?
   1. Never
   2. Occasionally
   3. Often

j. Has he/she ever seen a doctor about the cough?
   1. Yes
   2. No

Does this child cough during or shortly after vigorous exercise?
   1. Yes, usually
   2. Yes, occasionally
   3. No

8a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 9a

IF **YES** TO QUESTION 8A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: ~

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ _ months

OR: check here if doctor never said he/she had asthma: ~

e. **During the past year**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past year**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

9a. Has your child ever had bronchitis?

1. Yes
2. No . . . SKIP TO QUESTION 10a

IF **YES** TO QUESTION 9a:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last episode occurred?

_____ months

OR: check here if child still has bronchitis ___

d. How old was this child when you were first told by a doctor that he/she had bronchitis?

_____ months

OR: check here if doctor never said he/she had bronchitis___

e. How often has this child had bronchitis?

1. one episode only
2. 2-3 episodes
3. 4 or more separate episodes
4. almost constantly

f. During the past year, how much trouble did he/she have with bronchitis?

1 2 3 4 5

None A great deal

g. During the past year, did this child take any medicine for bronchitis?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 254

10a. Has your child ever had croup?

1. Yes
2. No . . . SKIP TO QUESTION 11a

IF **YES** TO QUESTION 10a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of croup?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

11a. Has your child ever had bronchiolitis, or any wheezing illness in the first year of life not due to asthma?

1. Yes
2. No . . . SKIP TO QUESTION 12a

IF **YES** TO QUESTION 11A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

12a. Has your child **ever** had pneumonia?

1. Yes
2. No . . . SKIP TO QUESTION 13

IF **YES** TO QUESTION 12a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

13a. Was this child breast fed?

1. Yes
2. No . . . SKIP TO QUESTION 14

IF **YES** TO QUESTION 13a:

b. For how many months was this child breast fed?

1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

14a. Has the mother smoked at all since this child was born?

1. Yes
2. No . . . SKIP TO QUESTION 15a

IF **YES** TO QUESTION 14a:

b. For how many months did the mother smoke since this child was born?

_____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES)

_____ cigarettes
_____ pipes
_____cigars
_____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?

Never
Occasionally
Frequently

15a. Has the father smoked at all since the child was born?

1. Yes
2. No . . . SKIP TO QUESTION 16

IF **YES** TO QUESTION 15a:

b. For how many months did the father smoke since this child's birth?

_____ months

c. On the average, how many of each of the following did he smoke per day during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES).

_____ cigarettes
_____ pipes
_____ cigars
_____ non-tobacco cigarettes

d. How often has the father smoked in the same room with this child?

1. Never
2. Occasionally
3. Frequently

16. Did any other household member regularly smoke in the house since this child's birth?

1. Yes
2. No

17. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

18. How many brothers and sisters (including half siblings) does this child have?

_____

19a. Are there any other children living in your household **besides** this child and all of his/her siblings?

1. Yes
2. No . . . SKIP TO QUESTION 20

IF **YES** TO QUESTION 19a:

b. How many children other than this child and his/her siblings live in your house?

_____

20. Do you have any pets?
1. Yes
2. No

1❑ Dogs #:_____
2❑ Cats #: _____
3❑ Other #:_____

21. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).

1. steam or hot water
2. central gas furnace
3. wall or floor gas furnace
4. electric
5. other
6. don't know

OUTPATIENT RESPIRATORY PROPHYLAXIS

22. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?
1. Yes
2. No

23. Did this child receive a flu shot?
1. Yes
2. No

OUTPATIENT RESPIRATORY SUPPORT

24a. Is your child on any oxygen therapy (oxygen tank at home)?

1. Yes
2. No

IF **YES** TO QUESTION 24a:

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

*lpm = liters per minute

25. Is your child taking any medicines for asthma or wheezing?

1. Yes
2. No
3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as:* ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other _____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

THANK YOU FOR YOUR COOPERATION

SUPPORT FOLLOW ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED AT 18-22 MONTH FOLLOW UP VISIT

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing concerns your child may have.

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

4a. Has his/her chest ever sounded wheezy or whistling?
   1. Yes
   2. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?

1	2	3	4	5
Very rarely				On Most days

e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing _

g. Has this child's wheezing/whistling occurred as attacks?
   1. Yes
   2. No

h. Has this child ever been awakened at night by wheeze or by shortness of breath?
   1. Yes
   2. No

i. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

j. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

5. Does this child's chest sound wheezy or whistling during or shortly after vigorous exercise or crying?
   1. Yes, usually
   2. Yes, occasionally
   3. No

6a. Has he/she ever had episodes of shortness of breath or chest tightness?
   1. Yes
   2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6A:

b. Has this ever occurred when the child is at rest?
   1. Yes
   2. No

c. During the past year, how many episodes did he/she have?

1 2 3 4 5
Few — Very many

d. How old was this child when he/she had the first such episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

OR: check here if the child still has condition: _

f. Has the child's chest ever sounded wheezy or whistling during episodes of shortness of breath or chest tightness?
   1. Yes
   2. No

g. Has he/she ever seen a doctor for shortness of breath or chest tightness?
   1. Yes
   2. No

h. Has this child ever taken any medicine for shortness of breath?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

7. Has this child ever had a cough when he/she did not have a cold?
   1. Yes
   2. No . . . SKIP TO QUESTION 6

IF **YES** TO QUESTION 5a

b. At what time of the day has this cough usually occurred? (CIRCLE ALL THAT APPLY) 1.
   1. In the morning, shortly after rising
   2. Later in the day
   3. During the night
   4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?
   1. Yes
   2. No

d. How often has this child been bothered by coughing?

1	2	3	4	5
Very Rarely				On most days

e. How old was the child when he/she first began to cough?
   ____ months

   OR: check here if child is still coughing: _

f. How old was this child when he/she stopped coughing?
   _____ months

g. Has the cough usually been dry or loose?
   1. Dry
   2. Loose

h. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?
   1. Yes
   2. No

i. How often has your child raised phlegm, sputum or mucus when coughing?
   1. Never
   2. Occasionally
   3. Often

j. Has he/she ever seen a doctor about the cough?
   1. Yes
   2. No

Does this child cough during or shortly after vigorous exercise?
   1. Yes, usually
   2. Yes, occasionally
   3. No

8a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 9a

IF **YES** TO QUESTION 8A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: _

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ _ months

OR: check here if doctor never said he/she had asthma: _

e. **During the past year**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past year**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

9a. Has your child ever had bronchitis?

1. Yes
2. No . . . SKIP TO QUESTION 10a

IF **YES** TO QUESTION 9a:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last episode occurred?

_____ months

OR: check here if child still has bronchitis ___

d. How old was this child when you were first told by a doctor that he/she had bronchitis?

_____ months

OR: check here if doctor never said he/she had bronchitis___

e. How often has this child had bronchitis?

1. one episode only
2. 2-3 episodes
3. 4 or more separate episodes
4. almost constantly

f. During the past year, how much trouble did he/she have with bronchitis?

1 2 3 4 5

None A great deal

g. During the past year, did this child take any medicine for bronchitis?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 254

10a. Has your child ever had croup?

1. Yes
2. No . . . SKIP TO QUESTION 11a

IF **YES** TO QUESTION 10a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of croup?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

11a. Has your child ever had bronchiolitis, or any wheezing illness in the first year of life not due to asthma?

1. Yes
2. No . . . SKIP TO QUESTION 12a

IF **YES** TO QUESTION 11A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

12a. Has your child **ever** had pneumonia?

1. Yes
2. No . . . SKIP TO QUESTION 13

IF **YES** TO QUESTION 12a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

13a. Was this child breast fed?

1. Yes
2. No . . . SKIP TO QUESTION 14

IF **YES** TO QUESTION 13a:

b. For how many months was this child breast fed?

1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

14a. Has the mother smoked at all since this child was born?

1. Yes
2. No . . . SKIP TO QUESTION 15a

IF **YES** TO QUESTION 14a:

b. For how many months did the mother smoke since this child was born?

_____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES)

_____ cigarettes
_____ pipes
_____cigars
_____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?

Never
Occasionally
Frequently

15a. Has the father smoked at all since the child was born?

1. Yes
2. No . . . SKIP TO QUESTION 16

IF **YES** TO QUESTION 15a:

b. For how many months did the father smoke since this child's birth?

_____ months

c. On the average, how many of each of the following did he smoke per day during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES).

_____ cigarettes
_____ pipes
_____ cigars
_____ non-tobacco cigarettes

d. How often has the father smoked in the same room with this child?

1. Never
2. Occasionally
3. Frequently

16. Did any other household member regularly smoke in the house since this child's birth?

1. Yes
2. No

17. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

18. How many brothers and sisters (including half siblings) does this child have?

_____

19a. Are there any other children living in your household **besides** this child and all of his/her siblings?

1. Yes
2. No . . . SKIP TO QUESTION 20

IF **YES** TO QUESTION 19a:

b. How many children other than this child and his/her siblings live in your house?

_____

20. Do you have any pets?
1. Yes
2. No

1❑ Dogs #:_____
2❑ Cats #: _____
3❑ Other #:_____

21. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).

1. steam or hot water
2. central gas furnace
3. wall or floor gas furnace
4. electric
5. other
6. don't know

OUTPATIENT RESPIRATORY PROPHYLAXIS

22. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?
1. Yes
2. No

23. Did this child receive a flu shot?
1. Yes
2. No

OUTPATIENT RESPIRATORY SUPPORT

24a. Was your child ever on any oxygen therapy (oxygen tank at home)?

1. Yes
2. No

IF **YES** TO QUESTION 24a:

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

*lpm = liters per minute

25. Is your child taking any medicines for asthma or wheezing?

1. Yes
2. No
3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as*: ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other _____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

ATOPY HISTORY

26. **During the past year**, for how many days has this child been unable to do his/her usual activities because of illnesses such as chest (not head) colds, bronchitis, asthma or pneumonia?

_____ days

27. How many head colds (common colds) **per year** does this child usually have?

1. Few (0-3 per year)
2. Some (4-5 per year)
3. Frequent (6-9 per year)
4. Constant (more than 9 per year)

28a. Has your child **ever** had hay fever or any other condition that makes his/her nose runny, stuffy, or itchy **apart** from colds?

1. Yes
2. No . . . SKIP TO QUESTION 29

IF **YES** TO QUESTION 28a:

b. How old was your child when you first noticed this condition?

_____ months

c. How old was this child when he/she stopped having this condition?

_____ months

OR: check here if child still has condition ~

d. When this child has the runny or stuffy nose, does he/she also usually:

Cough?	1. Yes 2. No
Wheeze?	1. Yes 2. No
Have shortness of breath?	1. Yes 2. No

29. Has this child **ever** had allergies which cause nose, eye or lung problems?

1. Yes
2. No

30. Has a doctor **ever** told you that this child had sinus trouble?

1. Yes
2. No

31a. Has this child **ever** been allergic to any food?

1. Yes
2. No

b. Has he/she **ever** been allergic to any medicine?

1. Yes
2. No

32a. Has this child **ever** had eczema (allergic skin rash)?

1. Yes

2. No . . . SKIP TO QUESTION 33a

IF **YES** TO QUESTION 32A:

b. Has a doctor told you this child had eczema?
1. Yes
2. No

c. At what age did the eczema begin?
_____ months

d. How old was this child when he/she last had eczema?
_____ months

OR: check here if child still has eczema ~

33a. Was this child breast fed?
1. Yes
2. No . . . SKIP TO QUESTION 34

IF **YES** TO QUESTION 33a:

b. For how many months was this child breast fed?
1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

34. At what age was formula introduced?
1. Never
2. less than 1 month
3. 1-3 months
4. 4-6 months
5. more than 6 months

35. At what age was cow's milk (nonformula) started?
1. Never
2. Less than 1 month
3. 1-3 months
4. 4-6 months
5. 7-9 months
6. 9-11 months
7. 12 or more months

36. At what age did he/she begin to receive table foods?
1. less than 1 month
2. 1-3 months
3. 4-6 months
4. 7-9 months
5. more than 9 months

THANK YOU FOR YOUR COOPERATION

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Antenatal Paper
Date: Tuesday, February 02, 2010 11:12:05 AM

I would send that to John McGrath and Mona and ask them

Catherine Y Spong MD
Chief, Pregnancy and Perinatology Branch
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Phone 301 435 6894 or 301 496 5575
Fax 301 496 3790
email spongc@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, February 02, 2010 11:10 AM
To: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: Antenatal Paper

He has two paragraphs in the paper. Let me know if they are ok or if we need to send through clearance again.
Results:

We estimated the cost of the consent process using the data from the questionnaire. Because the time needed to obtain consent was not a continuous variable, the costs were calculated as ranges. It took between 1776 and 3284 hours to enroll 611 infants. Based on the standard coordinator salary for the Network at the time of the trial, this represents between $65,513 and $124,822 enrollment costs. Assuming equivalent enrollment for the part of the trial not covered by this secondary study, the total costs for the trial would have been between $140,852 and $268,367.

DISCUSSION

To our knowledge this is the first study to evaluate the time and efforts required to approach and obtain antenatal consent from parents for the enrollment of their unborn infants. Our results reveal that 5 families needed to be identified and screened for every one infant successfully enrolled. Only 47.7% of women consented went on to deliver infants in the study window. Though the time needed to obtain consent was collected as a discrete variable, we found that the median was between 30 minutes and 1 hour. Multiplying these bounds by the number of women approached for each enrolled infant (3.6) yields a value for coordinator time required to obtain an

enrolled infant at between 1.8 and 3.6 hours, compared to the original trial design of 1.5 to 2 hours. Assuming that the enrollment rate of the SUPPORT trial was equivalent before data collection for the antenatal consent study began suggests that over 2400 hours were spent screening greater than 6000 women and approaching nearly 4800 for consent to enroll 1316 infants in the SUPPORT trial. This estimate includes time spent approaching women who did not consent and consenting women who did not deliver in the window. It does not account for time spent screening women who were not approached for consent.

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Tuesday, February 02, 2010 11:06 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Antenatal Paper

I don't know really whose permission – I would talk with GMB and see what they say

Catherine Y Spong MD
Chief, Pregnancy and Perinatology Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health
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Fax 301 496 3790
email spongc@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, February 01, 2010 5:04 PM
To: Spong, Catherine (NIH/NICHD) [E]
Subject: Fw: Antenatal Paper

We need Mona's permission/sign off to do this, right??

From: Rich, Wade <wrich@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Finer, Neil <nfiner@ucsd.edu>; Gantz, Marie <mgantz@rti.org>
Sent: Mon Feb 01 11:01:10 2010
Subject: Antenatal Paper

Hi Rose,

At the request of the reviewers, I would like to include the budgeted time for consent for SUPPORT in my paper and compare it to the time it actually took. Would that have been broken out on a budget somewhere ?

Wade

From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: SUPPORT Secondary
Date: Tuesday, February 01, 2005 12:51:17 AM

I think I voted YES
BJS

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT protocol
Date: Monday, January 31, 2005 10:37:09 AM

At this point I think Lisa would be fine.
Thanks Rose

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Neil Finer (nfiner@ucsd.edu)
Sent: Monday, January 31, 2005 5:44 AM
Subject: FW: SUPPORT protocol

Neil
FYI – here was the original "voting item." You are correct, share the protocol with Dr. Askie. Are there other folks besides those listed in the email below that would be involved in the prospective meta-analysis? IF so, I think we should inform the steering committee.
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD)
Sent: Wednesday, October 06, 2004 7:52 AM
To: Abbot Laptook (E-mail); Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (E-mail)
Cc: 'petrie@rti.org'; 'bkh@rti.org'
Subject: SUPPORT protocol

Neil Finer has a number of requests for the SUPPORT protocol from other investigators - primarily those involved with POST ROP, BOOST II. He would like to provide it to them. Neil wants to keep them involved and informed as we are going to use the same oximetry intervention, developed by us, and we will be able to perform a prospective meta analysis using all the studies if we adhere to this. This would be very powerful and could represent 5000 infants. The major collaborators are William Tarnow-Mordi, Cynthia Cole and Lisa Askie.
Please send me a YES/NO vote by October 12, 2004 to provide the protocol (once finalized) to these investigators.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
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301-435-7909

301-496-3790 (FAX)

From: Higgins, Rosemary (NIH/NICHD)
To: petrie@rti.org
Subject: FW: SUPPORT Follow On Study and K23 application
Date: Monday, January 31, 2005 3:47:00 PM
Attachments: SUPPORT Follow-on Study 10-1.doc
Costs for Follow-on.xls
Budget Justification.doc
Appendix A.doc
Appendix B.doc
Appendix C.doc

Carolyn
Can you send this to the advisory board for input??
Thanks
Rose

-----Original Message-----
From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Tuesday, October 12, 2004 4:12 PM
To: 'nfiner@ucsd.edu'; Higgins, Rosemary (NIH/NICHD)
Subject: FW: SUPPORT Follow On Study and K23 application

Neil,

Thank you for contacting me. I suspect this email was one of the ones you lost. I did send this out last Monday. Here is a copy.

When I sent this out on 10/3, I got an out of office reply from Rose. I hope she received her copy. I included her on this email just in case.

Let me know if I can answer any questions.

Thank you,

Tim

-----Original Message-----
From: Stevens, Timothy
Sent: Sunday, October 03, 2004 10:06 PM
To: 'nfiner@ucsd.edu'; 'higginsr@mail.nih.gov'
Cc: Phelps, Dale
Subject: RE: SUPPORT Follow On Study and K23 application

Hi Neil and Rose,

Here is a copy of the most current version of the SUPPORT Trial Pulmonary Outcome Follow-on Study. I have included an updated budget that outlines the total anticipated cost and the potential for K23 funds to offset a portion of the study costs. A brief budget justification and 3 appendices to the proposal are included as well.

Thank you for considering this project. I am very excited to move it forward. Please let me know if I can answer any questions.

Thanks

Tim

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, September 30, 2004 7:24 PM
To: Stevens, Timothy
Subject: RE: SUPPORT Follow On Study and K23 application

Tim
We will be reviewing your protocol on Oct 14. Please send me the most current version and budget etc.
Regards
Neil Finer

-----Original Message-----
From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Tuesday, September 28, 2004 4:41 AM
To: 'nfiner@ucsd.edu'
Cc: Sgroi, Vanessa
Subject: RE: SUPPORT Follow On Study and K23 application

Neil,

I have not received the signed letter yet. To be on the safe side would mind printing the letter, signing it and giving it to Dale Phelps, Carl D'Angio or Ronnie Guillet (Rochester people at the NICHD meetings) to bring back to Rochester with them. The grant is due out on Friday 10/1. Can we contact your office to obtain your biosketch and other support information to be included in the grant.

Thanks

Tim

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Friday, September 17, 2004 3:27 PM
To: Stevens, Timothy
Subject: RE: SUPPORT Follow On Study and K23 application

Here is the letter we sent.
Neil Finer

-----Original Message-----
From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Tuesday, September 14, 2004 9:50 AM
To: 'Neil Finer'
Cc: Phelps, Dale
Subject: RE: SUPPORT Follow On Study and K23 application

Neil,

As I mentioned, I am preparing a K23 application using the SUPPORT Follow on Study of Pulmonary Outcomes as the central project of the Career Development Award. I realize that the Network has not fully committed to this study and that the study may still fail to be approved. However, due to the time lag in gaining funding from a K23 award, I am going forward with the K23 submission at this time so that K23 funding would be available by 7/1/05 to

support the Follow on Study.

Would you be willing to write a letter describing the progress of the Follow on Study through the NICHD Network review process? I took the liberty of drafting a letter; please feel free to edit the letter as necessary. I would like to receive the letter by 9/21 if at all possible so that it may be included in the institutional grant sign off packet.

Dale is one of the mentors for the Career Development Award and will be writing a letter in that capacity. I've attached an email correspondence string between Dale and Rose that states it is acceptable for you to submit a supporting letter like the draft letter attached. If the Follow on Study is approved, Rose will write the formal letter to the K23 committee.

Please let me know if I may answer any questions.

I really appreciate your help.

Tim Stevens

****

Timothy P. Stevens, MD
Assistant Professor of Pediatrics
Division of Neonatology
Golisano Children's Hospital at Strong
University of Rochester
601 Elmwood Avenue, Box 651
Rochester, NY 14642
Phone: 585-275-2972
Fax: 585-461-3614
Email: timothy_stevens@urmc.rochester.edu

-----Original Message-----
From: Phelps, Dale
Sent: Friday, September 10, 2004 3:37 PM
To: Stevens, Timothy
Subject: FW: K23 documentation

additional fodder for the reworking.
I read this as quite helpful!
Print and save this. You'll want to be able to send it to Neil so that he knows it is ok to do a letter. I'll work on my letter for you.
Dale

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 10, 2004 8:00 AM
To: Phelps, Dale
Subject: RE: K23 documentation

Dale
Either or both you and Neil are free to write letters describing where the proposal is in the network process. If this becomes "approved" prior to the study section meeting, I am happy to provide "official" NICHD documentation.
Thanks for asking!

Rose

-----Original Message-----
From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Thursday, September 09, 2004 6:22 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: K23 documentation

Hi Rose,

Tim Stevens (faculty here) is preparing his K23 (scientific project is a secondary in SUPPORT) to go in for the Oct. 1 deadline. We recognize that the Network has not yet approved this project (I understand it is on its way to the Protocol Committee because of costs), and there is no guarantee of funding, even if the protocol committee approves it.

However. Something needs to go in with the K23 to document how far Tim has gotten with the proposal within the Network so that his proposal does not appear naive or hypothetical (he does have a section for alternatives if it does not materialize).

The question is, "What" ?
Letter from me saying what part of the process he has been through ?

Letter from Neil Finer?
Are either of us allowed to write a letter?

I know you are not allowed to write a letter.

Before I write something, or we ask Neil to, I thought we should ask you what is permissible, allowable, advisable....

Dale

Dale L. Phelps, MD
Professor of Pediatrics and Ophthalmology
Pediatrics, Box 651
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(585) 275-2972
FAX (585) 461-3614

NICHD SUPPORT Trial Follow-on Study of Outpatient Pulmonary Outcomes

University of Rochester
Golisano Children's Hospital at Strong

Timothy P. Stevens, MD
Peter Szilagyi, MD, MPH
Dale Phelps, MD

Proposal Updated: October 1, 2004

Contact Information:

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Email: timothy_stevens@urmc.rochester.edu

A. ABSTRACT

Statement of Problem Premature infants have a greater risk for wheezing and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor for later wheezing, the etiology of recurrent wheezing in formerly premature infants is not known.

Hypotheses The goal of the clinical project detailed here is to understand better the antecedents of recurrent wheezing among preterm infants during early childhood by evaluating the effect of treatment with different levels of targeted oxygen saturation in the immediate neonatal period. **The overarching hypothesis is that premature infants exposed to supplemental oxygen suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater symptomatic airway dysfunction when challenged with subsequent environmental or infectious exposures.**

Hypothesis #1- Relative to infants managed with a higher SpO2 range, infants who are managed with a lower targeted SpO2 range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' corrected age (CA) whether they develop CLD or not.

Hypothesis #2- Relative to infants managed with prophylactic surfactant and conventional ventilation, infants who are managed with the early use of CPAP and a permissive ventilator strategy will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' CA whether they develop CLD or not.

Design

Longitudinal follow-up of infants enrolled in the SUPPORT Trial to determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the prevalence of recurrent wheezing and volume of outpatient pulmonary care in the first 18 months' CA.

Definition of outcomes:

A) Parental Report of Wheezing
B) Physician Diagnosed Wheezing.
C) Volume of Outpatient Pulmonary Care including number of pulmonary medications, office and emergency room visits and re-hospitalizations for respiratory illnesses.

Ascertainment of outcomes:

Outcomes will be measured at 4 time points in the first 18-22 months' CA as follows:

1. NICU discharge -baseline interview at to obtain family and environmental history
2. Six months' CA - telephone interview to ascertain prevalence of wheezing and obtain interval history of need for pulmonary care.
3. Twelve months' CA - telephone interview as at 6 months'
4. 18-22 months' CA- Prior to NICHD follow-up clinic visit, a telephone interview to ascertain prevalence of wheezing and obtain interval history of need for pulmonary care will be administered and primary care physician contact information collected for outpatient office chart review.
5. Outpatient chart review- data extraction from patient outpatient medical record.

Anticipated Results

We anticipate that, for infants who develop CLD and those who do not, treatment with a lower vs. higher targeted oxygen saturation range will result in less frequent episodes of wheezing and less need for outpatient pulmonary care in the first 18-22 months' CA.

Benefits and Risks

The proposed SUPPORT Follow-on Pulmonary Outcome Study will directly measure symptomatic airway dysfunction and outpatient pulmonary morbidity in infants treated with either a higher vs. lower targeted oxygen saturation. These data will provide important insight into the effect of different levels of supplemental oxygen exposure on airway growth and development in formerly premature infants. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the neurodevelopmental follow up visit. We anticipate no risk to the patient of this observational follow-on study.

B. STATEMENT OF THE PROBLEM

Premature infants have a greater risk for wheezing and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor for later symptomatic airway dysfunction, the etiology of recurrent wheezing in formerly premature infants is not known.

C. HYPOTHESES

The overarching hypothesis is that premature infants exposed to supplemental oxygen and, to a lesser extent, mechanical ventilation, in the neonatal period suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction and respiratory symptoms when challenged with subsequent environmental or infectious exposures.

Specific Hypotheses:

Hypothesis #1- We hypothesize that relative to infants managed with a higher SpO2 range, infants managed with a lower SpO2 range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care at 18-22 months' CA.

Hypothesis #2- We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

Hypothesis #3- We hypothesize that **among infants with CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

Hypothesis #4- We hypothesize that **among infants without CLD**, infants managed with early use of CPAP and permissive ventilator strategy relative to infants managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

D. SPECIFIC AIMS

The goal of this project is to understand better the etiology of recurrent wheezing among formerly premature infants during early childhood by examining the interaction of oxygen exposure (targeted SpO2 range), surfactant therapy and early nasal CPAP in the newborn period.

SA#1 - Measure the effect of lower vs. higher targeted SpO2 on the prevalence of recurrent wheezing and volume of outpatient pulmonary care among infants born $24^{0/7}$ - $27^{6/7}$ weeks' gestation during the first 18-22 months' CA.

SA#2 - Measure the effect of early CPAP and permissive ventilator strategy compared with prophylactic surfactant and traditional ventilator strategy on the prevalence of recurrent wheezing and volume of outpatient pulmonary care among infants born 24-27 weeks' gestation during the first 18-22 months' CA.

SA#3 – Among infants who develop CLD, determine whether CLD is milder in infants managed with low compared with high targeted SpO2 by measuring recurrent wheezing and volume of outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

SA#4 – Among infants who do not develop CLD, determine whether pulmonary outcome is better for infants managed with a low compared with high targeted SpO2 range by measuring the prevalence of recurrent wheezing and need for outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory

strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

E. RATIONALE/JUSTIFICATION

Although synergy in producing airway injury may exist between oxygen toxicity and mechanical forces applied to the lung, animal and human data suggest that exposure to high concentrations of supplemental oxygen alone is sufficient to cause airway narrowing and greater reactivity to subsequent challenges. Understanding the relative contributions of oxygen toxicity and mechanical forces on airway growth and development may facilitate development of targeted therapies for preventing or reducing symptomatic airway dysfunction in premature infants.

Why measure recurrent wheezing and outpatient pulmonary care as an outcome from a clinical NICU interventional trial?

1) Important information will be available on the effect of oxidant gas exposure on airway development and later symptomatic airway dysfunction. Exposure to oxidant gas has been causally linked with later wheezing. Existing data on the relationship between supplemental oxygen therapy and wheezing come from longitudinal cohort studies, a design that suffers from intrinsic limitations that make controlling for potential confounders of respiratory outcome difficult. By randomizing infants to higher vs. lower target saturation ranges, and thereby presumably higher or lower concentrations of inspired oxygen, *the SUPPORT Trial creates a unique, and perhaps the only, opportunity to evaluate the effect of different levels of supplemental oxygen on subsequent symptomatic airway dysfunction and need for outpatient pulmonary care after NICU discharge.*

2) Using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care can be directly quantified, allowing assessment of whether infants both with and without CLD have improved pulmonary health as a result of the study intervention.

3) The incidence of CLD, defined as an oxygen requirement at 36 weeks' PMA, is an incomplete measure of pulmonary outcome in formerly premature infants during early infancy. CLD as defined above reflects alveolar gas diffusion and NICU oxygen needs. However, outpatient pulmonary morbidity for formerly premature infants is often airway related, involving wheezing either as a primary symptom such as bronchiolitis or as a complicating symptom of lower respiratory tract infection such as pneumonia. The studies proposed here will directly measure the effect of a randomized NICU-based clinical intervention on symptomatic airway dysfunction and outpatient pulmonary morbidity.

4) The risk of a negative trial is reduced. Because the diagnosis of CLD does not completely predict need for outpatient pulmonary care, clinically significant improvements in pulmonary morbidity may occur with minimal or no change in the incidence of CLD. This result has occurred in other interventional trials in which no difference in CLD were observed (12).

5) At present, there is no standard way to measure symptomatic airway dysfunction in premature infants in NICHD pulmonary intervention trials. There is need for a better measure to assess clinical pulmonary outcome to recognize and promote therapies that reduce need for outpatient care of former extremely premature infants.

6) By measuring outpatient pulmonary outcomes, the cost-effectiveness of the SUPPORT study interventions can be assessed. It is reasonable to expect that the SUPPORT Trial interventions will improve outpatient pulmonary outcomes for infants who ultimately develop CLD as well as those who do not. This proposed follow-on study collects the primary data necessary to quantify the cost-effectiveness of this therapy.

F. BACKGROUND / PREVIOUS STUDIES

Recurrent Wheezing In Preterm Infants is a Significant Public Health Problem

Outpatient pulmonary morbidity, especially recurrent wheezing and need for outpatient pulmonary care, is an understudied but clinically important outcome measure for former premature infants with and without CLD. Infants born weighing < 1500 grams (very low birth weight, VLBW) and especially infants born weighing < 1000 grams are at increased risk for small airway narrowing, airway hyperreactivity, wheezing, and nighttime cough (1-11). Up to 30-40% of formerly extremely premature infants have episodes of wheezing after NICU discharge with many requiring bronchodilators and frequent health care visits. Up to 40-50% of premature infants require re-hospitalization, mostly for treatment of respiratory illnesses (9;12;13). In analysis of cross sectional data from the National Maternal Infant Health Survey and 1991 Longitudinal Follow up Survey, the prevalence of asthma-like recurrent wheezing varied markedly with birth weight. Infants with normal birth weight (NBW, > 2500 grams) had a 6.7% prevalence of asthma compared to 10.9% of low birth weight infants (LBW, 1500-2499 grams) and 21.9% for VLBW (14). Mean per capital asthma related costs have been estimated to be 5 times greater for VLBW compared with NBW infants. The net effect is that VLBW infants, who comprise 2% of asthma patients, consume up to 7% of asthma-related therapy costs (14).

Animal Studies

Animal studies suggest that exposure of the premature lung to hyperoxia (without concomitant mechanical ventilation) for relatively brief periods is sufficient to cause airway remodeling and smooth muscle changes that predispose toward airway narrowing and hyperreactivity to subsequent environmental challenges (15-18). In a rhesus monkey model of asthma, Schlegle et al. exposed infant monkeys to repeated cycles of inhaled House Dust Mite Allergen (HDMA), ozone or filtered air. While repeated exposure to either ozone or HDMA had mild effects, exposure to cycles of ozone followed by HDMA resulted in asthma like changes with significant increases in serum IgE, serum histamine, peripheral eosinophilia and greater airway reactivity. Using supplemental oxygen rather than the stronger oxidant ozone, Schulman et al. found that exposure of newborn guinea pigs to 70% oxygen for 96 hours resulted in airway hyperreactivity at 2 and 9 days after the cessation of oxygen. In cell models, intracellular glutathione buffers airway cells against oxidant injury during hyperoxia (19;20). Although the critical period for lung development is comparatively brief in laboratory animals compared with human infants, the duration of hyperoxic exposure (and risk of oxygen toxicity) for treatment of neonatal lung disease may extend for much longer periods in premature infants known to be deficient in anti-oxidant systems such as intracellular glutathione.

Premature Infants <u>With CLD</u> Are At Greatest Risk For Recurrent Wheezing

Among premature infants, infants with bronchopulmonary dysplasia (BPD) are at highest risk for poor pulmonary outcome after NICU discharge. Infants with CLD have small airway compromise with decreased forced expiratory flow velocities, airway hyperreactivity, and increased functional residual volume suggesting airway obstruction (2;5;9;21-24). In a pulmonary follow up of infants with HMD or BPD, De Klein et al. found infants with BPD had reduced FEV1 at baseline while infants with RDS but not BPD had significant improvements in FEV1 following bronchodilator therapy. In this study, a history of recurrent wheezing predicted abnormal pulmonary function (25). In a recent study of infants with CLD, Robin et al. found that 50% of infants with CLD had symptoms of recurrent wheezing and 35% showed significant airway responsiveness to bronchodilators, evidenced by a 24% increase in forced expiratory flow velocity at 75% of expired forced vital capacity (FEF_{75}). This study demonstrated the relationship between recurrent wheezing as a clinical symptom and the physiologic measurement of airway obstruction. Infants with CLD and a history of recurrent wheezing showed greater expiratory flow limitation, hyperinflation, and airway responsiveness to albuterol compared to those without a history of recurrent wheezing (24).

Premature Infants Without CLD Have Significant Airway Dysfunction

Among VLBW infants who do not develop CLD, several studies of pulmonary outcome have found an association between neonatal oxygen exposure and increased prevalence of expiratory flow dysfunction and airway hyperreactivity (4;11;26-29). Some authors attribute reductions in airway function to intrinsically small airways as a consequence of poor intrauterine growth rather than superimposed airway injury or reactivity from neonatal respiratory disease (1;30). However, because small airways alone do not fully explain findings of airway hyperreactivity, other mechanisms of small airway dysfunction are necessary to explain respiratory symptoms.

Several pulmonary outcome studies have reported significant increases (2-fold or more) in airway obstruction among VLBW infants without CLD following exposure to as little as an FIO2 of 0.4 for 5 days (3;4;8;26). Not all studies have had similar results suggesting variability in effect or susceptibility of babies to oxygen exposure (31;32). In 1982, Coates et al. described increased small airway resistance at 10 year follow up of mildly premature infants (mean gestational age 31 weeks and birth weight 2000 grams) treated with a high oxygen (O2) regimen and those exposed to a low O2 regimen for the treatment of respiratory distress syndrome (RDS). Mechanical ventilation was not used in either group. Pulmonary function tests were performed on survivors receiving either the low or high supplemental oxygen regimen ten years after their initial illness. Infants treated with high levels of supplemental oxygen alone (no mechanical ventilation) had decrements in airway function similar to decrements in function reported for a historical cohort of RDS survivors treated with ventilation and high levels of supplemental oxygen. From these data, the authors concluded that neonatal exposure to high oxygen concentrations in the absence of mechanical ventilation is capable of causing long-term change in small airways (28). These studies suggest that use of lower supplemental oxygen concentration may improve respiratory health of infants who do not develop CLD.

Premature Infants Without CLD Have Increased Risk of Recurrent Wheezing and Need for Outpatient Pulmonary Care.

For VLBW infants without CLD, the prevalence of parental or physician reported wheezing is increased compared with term infants, with estimates of the prevalence of wheezing ranging from 10-38% (4;8). Prevalence of wheezing requiring medications is greater compared with term infants. VLBW infants have a 2-4-fold increase in respiratory related re-hospitalization rates compared with term infants (4;8;33-35). Although most studies have found the risk of recurrent wheezing remains elevated throughout childhood, an Australian longitudinal follow-up cohort of VLBW infants found the prevalence of wheezing remained elevated for 2 years then returned to baseline (32;36).

Prevalence of Symptomatic Airway Dysfunction in Formerly Preterm Infants During the Surfactant Era Remains High

With the advent of surfactant therapy, survival for small infants increased dramatically and the incidence of CLD changed minimally (37-40). Classic BPD evolved into the new CLD characterized by reduced alveolarization and more variable airway changes (41). Pulmonary follow up studies during the surfactant era showed reduced pulmonary morbidity in surfactant treated patients. Typical of these studies, Sell et al. found the incidence of asthma was significantly lower in infants given synthetic surfactant compared with those given air placebo. Pelkonen et al. performed PFT measurements on 40 children aged 7-12 years who were born before 30 weeks of gestation with an immature surfactant system, and were randomized to one of three treatment groups: prophylactic surfactant, rescue surfactant and placebo (air). Spirometric parameters of preterm born children were compared with those of 20 children born at term. Bronchial obstruction was found in 53% of the prophylactically treated group, in 36% of the rescue group, in 67% of the placebo group, and in 0% of the control group (42). A recent report suggests that the introduction of surfactant therapy markedly altered the pulmonary outcome of premature infants. Published in 2001, the Newborn Lung Function Project Group reported results of a prospective 12-year follow-up of VLBW infants following the introduction of surfactant therapy. Among infants with CLD, wheezing symptoms decreased from 50 to 16% from the period before compared with the period after surfactant therapy became available. However, among infants without CLD the prevalence of wheezing increased from 14% to 38% with the introduction of surfactant. These data suggest that surfactant therapy has an effect on outpatient respiratory health and underscores the need to

consider outpatient pulmonary outcomes in evaluating therapeutic strategies that potentially decrease surfactant replacement therapy.

CLD is an Incomplete Predictor of Outpatient Pulmonary Morbidity

Several authors have looked to respiratory symptoms and need for outpatient pulmonary care as outcome measures for neonatal lung disease (9;10;12;24). In 1988, from a retrospective chart review of 605 premature infants < 1500 grams, Shennan et al. found that the presence of BPD (oxygen requirement at 36 weeks PMA) had a 63% positive predictive value and a 90% negative predictive value for abnormal pulmonary outcome in the first 2 years of age. However, this study from before the era of exogenous surfactant therapy defined abnormal pulmonary outcome as death, oxygen requirement at 40 weeks PMA, 2 or more respiratory related hospital admissions, wheezing requiring drug therapy or persistent wheezing resulting in growth failure, handicap or hypotonia at 1 year of age. Such restrictive criteria for abnormal pulmonary outcome are likely to underestimate the burden of recurrent wheezing on former premature infants and their families. Several recent interventional studies show that CLD is an incomplete predictor of clinical wheezing and need for outpatient pulmonary care and suggest that differences in oxygen exposure or oxidant stress may affect pulmonary outcome without affecting the incidence of CLD.

Interventional Trials That Did Not Reduce CLD But Did Reduce Outpatient Pulmonary Morbidity.

Recent data in preterm infants treated with human recombinant superoxide dismutase (SOD) found that anti-oxidant therapy did not reduce the incidence of CLD. However, among infants < 27 weeks gestation SOD therapy resulted in significant reductions in the first year after NICU discharge in the number of emergency room visits and number of re-hospitalizations for respiratory problems and reductions in the need for bronchodilators suggesting a reduced prevalence of wheezing in patients treated with SOD (12). In a randomized, multi-center trial from Helsinki, N acetyl cysteine did not reduce the incidence of CLD. Outpatient pulmonary outcome of these patients has not been reported.

Treatment of Premature Infants With Higher Targeted Oxygen Saturations Is Associated with Poorer Pulmonary Outcome

In the STOP-ROP Study, infants exposed to higher levels of oxygen to achieve a targeted saturation of 96-99% compared with 89-94% had greater risk of adverse pulmonary events including pneumonia, chronic lung disease exacerbations and need for diuretics, oxygen and hospitalization at 3 months'' corrected age. *Although all infants in this study had CLD at enrollment, different targeted oxygen saturation were associated with large differences in pulmonary morbidity.* Adverse pulmonary outcomes occurred with differences in FIO2 of as little as 10% for patients treated with ventilation, CPAP or hood (36% $\pm$ 14% vs. 46% $\pm$ 20%, respectively for low vs. high saturation range) and 5% for infants treated with nasal cannula, (26% $\pm$ 6% vs. 31% $\pm$ 11%, respectively for low vs. high saturation range) (44). In a similar study, The Benefits of Oxygen Saturation Targeting (BOOST) Trial randomized infants < 30 weeks' gestation to higher (95-98%) or lower (91-94%) saturations ranges beginning at 32 weeks' PMA to determine whether infants managed with higher targeted saturation range showed better growth and neurodevelopment. As in the STOP-ROP study, need for oxygen therapy was prolonged. Trends towards an increased risk of pulmonary death and fewer outpatient office visits (median 27.5 vs. 31.3, $p < .11$) were seen in the lower targeted oxygen saturation group (13).

G. METHOD/ PROCEDURES

NICHD SUPPORT Trial Follow-on Study of Pulmonary Outcomes

G.1 Description of study design

This study will add an 18-22 month longitudinal, prospective follow-on study of surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial.

G.2 Definition of study population

Infants with gestational age of $24^{0/7}$-$27^{6/7}$ weeks' gestation by best obstetrical estimate.

Inclusion criteria:

- Full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Parents/legal guardians have provided consent for enrollment
- No known major congenital malformations
- Survival to hospital discharge

Exclusion Criteria

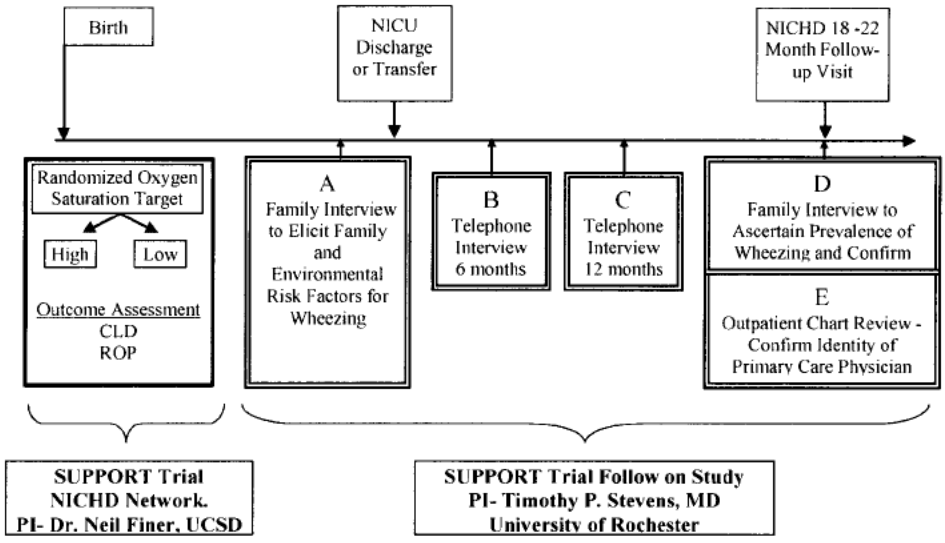
- Transport to the center after delivery
- Parents/legal guardians refuse consent
- Research apparatus/study personnel are not available.
- Gestational age $< 24^{0/7}$ or $\geq 28^{0/7}$ weeks' gestation

G.3 Description of study intervention

Before delivery, infants will be randomized to subsequent management with high vs. low target oxygen saturation according to the SUPPORT Protocol. The SUPPORT Follow-on Study proposed here begins just prior to NICU discharge (Figure 1).

SUPPORT Trial Follow-on Study

Figure 1. **Infants $24^{0/7}$-$27^{6/7}$ Weeks' Gestation**



"A" will be administered at NICHD Network Centers

"B-E" will be conducted long distance by University of Rochester research staff.

Fig 1, A. Parent (Guardian) Interview to Elicit Family and Environmental Risk Factors for Wheezing The family interview will be administered at each participating Network Center by site study nurses prior to NICU discharge or transfer. The questions are based on intake questions used by the Tucson Respiratory Study and are designed to elicit family history of asthma, atopy, and home environment and to identify likely care givers (Questionnaire in Appendix G). Consent for release of medical information will be obtained to facilitate contacting physician offices to obtain office data.

Fig 1, B. Telephone Interview at 6 months' CA – respiratory interval history

Fig 1, C. Telephone Interview at 12 months' CA – respiratory interval history

Telephone interviews will be undertaken at 6 and 12 months' to obtain limited interval history of respiratory problems including wheezing, medications used, and health services sought for respiratory related problems (Questionnaire in Appendix H).

Fig 1, D. Parental Interview to Ascertain Prevalence of Wheezing and Confirm Risk Factors This parent interview will also be administered by telephone, prior to the regularly scheduled 18-22 month NICHD developmental follow up clinic visit (an NICHD funded, ongoing program). Contacting parents prior to the office visit will help improve the Developmental Follow Up Clinic attendance rate and will allow the clinic visit to provide a back up means to contact the family. All telephone interviews, the 2 limited telephone interviews and the second family history interview at 18-22 months', will be conducted long distance from Rochester (see below). The interview questionnaires are based on questionnaires administered by the Tucson Respiratory Study at approximately one year of age (Questionnaire in Appendix I). Questions are designed to ascertain the frequency and severity of wheezing episodes. In addition, risk factors obtained at the 1st interview will be confirmed or updated.

Fig 1, E. Outpatient Chart Review - Confirm Identity of Primary Care Physician

To confirm results of physician report of wheezing obtained by telephone interview, patients undergoing telephone interview will have their primary care physician's medical record reviewed.

E.1 – Physician report of wheezing

E.2 – Frequency of outpatient pulmonary care. The volume of outpatient pulmonary care including outpatient primary care physician office visits, pulmonary specialty care, emergency room visits, hospitalizations and the number and duration of pulmonary medications will be obtained from primary care physician chart review. To help assure compliance by primary care office staff, a $25 honorarium will be offered for successful completion of the chart review form (45-47).

G.4 Precise definition of primary/secondary outcomes

1) Definition Of Parental Report Of Wheezing. The primary outcome will be parental report of recurrent wheezing, defined as more than 1 episode of wheezing, using questions adapted from the Tucson Children's Respiratory Study, questions validated in a large prospective birth cohort study of term infants (48-54) (Appendices G-I). The primary question used in the telephone interview for this project will be the same as the one used in the Tucson Children's Respiratory Study "Did your child have wheezing?" (48) Additional questions will be used to further characterize the wheezing episodes, identify wheezing associated with a viral illness (parental report of a "cold") and wheezing associated with environmental exposures. The prevalence of health services utilization (outpatient office visits for pulmonary care, ER visits, re-hospitalizations, bronchodilator therapy) for pulmonary reasons will also be collected during interviews. The Tucson study also ascertained frequency of office visits and use of respiratory medications. Of full term infants whose parents reported that their infant had an episode of wheezing, 40% had recurrent wheezing in the first 6 years compared with 22% of infants whose parents reported no episodes of wheezing in the first 3 years.

Parental Report of Wheezing Is A Reliable Outcome Measure of Airway Dysfunction

Evaluation of frequency and severity of respiratory symptoms and volume of pulmonary care has been used as the primary outcome in multiple follow up studies of term and premature infants (10;12;14;43). A recent review evaluated the value of respiratory symptom history ascertained by parental questionnaire in determining the risk for developing asthma in early childhood. By evaluating 9 large, longitudinal, full term birth cohort studies and reviewing the original questionnaire from 7 of these studies, Koopman found that the questions posed to parents

eliciting a history of wheezing in their infants were similar. Parental report of wheezing predicted an increased risk for later respiratory symptoms including asthma. In the studies proposed here, recurrent wheezing ascertained by parental report will be used as the primary outcome, rather than physiologic measurements of airway dysfunction, for several reasons (Table 3). Although the goal of using respiratory questionnaires in the studies proposed here is to measure pulmonary outcome, not to predict asthma, studies of asthma questionnaires and their ability to predict asthma demonstrates the validity of parental report of wheezing as an accurate measure of airway dysfunction.

Reasons to Use Parental Report of Wheezing as Primary Outcome Measure

- Parental interview can be performed more readily on large numbers of patients. The validity of this approach has been shown in several longitudinal studies including The Tucson Respiratory Study, upon which the interview questions are based.
- Recurrent wheezing is highly correlated with changes on pulmonary function testing. In a study of infants with CLD, a history of recurrent wheezing was associated with greater expiratory flow limitation, hyperinflation and airway responsiveness to albuterol on pulmonary function testing compared to those without a history of recurrent wheezing (24).
- Parental recall of respiratory illnesses has been shown to correlate strongly with review of medical office records. For asthma and bronchitis in the past year, Pless et al. found good agreement between recall of 288 parents and physician office chart review. Parental education and occupation were not predictive of a parent's ability to recall the illness (55). In an assessment of parental recall done to evaluate minor injury in children, Harel found recall declined with time, with the best recall occurring in the first 3 months' after injury with further decline after 6 months' from the time of the injury (47;56;57).

Advantages of Conducting Telephone Interviews From a Single Center

Conducting the telephone interviews from Rochester will:

1) require less effort from the individual Network Centers (Network Centers may assist in tracking families)
2) allow standardization of the telephone interview by a core group of trained interviewers
3) blind the telephone interviewer to the SUPPORT Trial study group designation
4) reduce the cost of the study by consolidating the telephone training and follow up at one site.

2) Definition Of Physician Diagnosed Wheezing. A secondary outcome will be physician report of recurrent wheezing, defined as more than 1 episode of wheezing. Physician diagnosed wheezing will be collected by parental report during telephone interviews using the question "Did a doctor tell you your child had wheezing?" and "Where did you see that Doctor, primary care, emergency room, hospital or other?" In addition, review of the primary care physician medical chart will be undertaken to identify episodes of physician documented wheezing.

3) Definitions of Secondary Outcomes - Measures of Volume of Outpatient Pulmonary Care

Important secondary outcomes of outpatient pulmonary morbidity will be collected (Table 1).

Table 1. ***Secondary Outcomes, Covariates and Sources***	
Outcomes	**Source**
Secondary Outcomes	
Number and duration of outpatient pulmonary medications including bronchodilator, diuretic, methylxanthine, and inhaled and systemic steroid therapy.	Family interview, primary care chart review
Number of office visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of emergency room visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of re-hospitalizations for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Growth at 18 months' CA (height, weight and head circumference)	NICHD follow up clinic data

Data Collection: Ascertainment of Outcomes - Field Work

Ascertainment of Wheezing and Outpatient Pulmonary Morbidity By Telephone Interview.
There will be 4 parental interviews over 18-22 months', one prior to NICU discharge and 3 subsequent telephone interviews at 6 month intervals to collect data on the prevalence of recurrent wheezing, need for outpatient pulmonary care, and relevant environmental and family history covariates (Figure 1, A-D above). Based on review of longitudinal studies of full term infants in which follow up patient contacts occurred quarterly to once every 18 months', a 6 month interval for follow up patient contacts is planned in an effort to reduce parental recall omissions which are more likely to occur with less frequent follow up (43;56). The 4 interviews are designed to collect the primary and secondary outcomes of the follow-on study. Other inpatient and outpatient data will be collected as part of the NICHD Neonatal Research Network Generic Database (GDB) and Follow-up Program.

The University of Rochester Neonatology Research Group has conducted similar telephone interview designs as part of an ophthalmologic outcome study of patients enrolled in a randomized trial of cryotherapy to treat ROP and a 15-year, longitudinal neurological assessment conducted by telephone survey among 132 infants treated with surfactant. Telephone follow up rates were 96% follow up at 7 years and 95% follow up at 15 years (58). In the study proposed here, the University of Rochester Health Services Research Group (HSR Group), will conduct the telephone interviews.

In telephone follow up surveys conducted by the HSR Group, follow up rates at 12 months' have exceed 75% in populations at high risk for being lost to follow up (59-65). The Rochester HSR Group has over 2,500 square feet of newly renovated space. Under the direction of Drs. Jonathan Klein and Peter Szilagyi, the HSR group includes sufficient space and all appropriate equipment and personnel to perform telephone interviews and database management for the project presented here. The HSR Group will conduct 3 telephone interviews from Rochester. Drs. Peter Szilagyi and Jonathan Klein, co-directors of the HSR Group, are mentors for Dr. Stevens' K23 Patient Oriented Research Award application. Drs. Klein and Szilagyi will work with Dr. Stevens and Dr. Phelps in the implementation and management of the tracking and respiratory questionnaire program. To facilitate tracking and record keeping, Dr. Stevens will design and write a database to track enrolled patients and their contact information, next scheduled interview, and record answers to phone interview questions. Each interview will close with a question as to whether the family plans a new address or phone number prior to the next interview. The names and phone number of a friend or relative and their primary care physician will be sought so that they may be contacted in the event that contact with the patient is lost. By interviewing families every 6 months', a higher follow up rate will be achieved because family contact information will not become so out of date that the family is lost or that re-contacting them is inefficient. We anticipate that each interview will require 2 hours of staff time, with 20-30 minutes to conduct the interview and 90 minutes to contact family and enter data.

Interview Instruments – (Appendices A-C) Questionnaires based on the Tucson Children's Respiratory Study, a well validated questionnaire used in a large longitudinal cohort study that followed healthy full term infants from birth to over 20 years of age. The questionnaires have been updated to reflect currently available respiratory medications and modified to address the health issues that are faced by formerly premature infants such as use of palivizumab for RSV prophylaxis. In addition, the questionnaires are designed to elicit a thorough history of possible covariates, such as environmental and infectious exposures and family histories of atopy, asthma or respiratory disease.

Physician Office Records Assessment of Wheezing and Outpatient Pulmonary Morbidity Physician office charts will be reviewed to determine physical findings of wheezing, medication use and respiratory related hospitalization history. For primary care pediatricians, the family's consent authorizing release of medical information and an office contact questionnaire will be mailed or faxed to the provider. The questionnaire will be based on a similar document used by the Rochester Research Group to obtain medical information on respiratory issues. To help assure compliance with completing the questionnaire, a $25 honorarium will be offered to the office staff.

Data Collection: Ascertainment of Environmental and Genetic Covariates

Ascertainment of important environmental exposures and genetic risk factors that might confound the relationship between supplemental oxygen exposure and recurrent wheezing will be obtained along with the primary outcome during the same telephone and family interviews (Table 2). A second follow-on study to the SUPPORT Trial, not affiliated with the studies proposed here, is being independently proposed by other investigators to study specific genetic markers that predict greater risk of CLD. Although synergy between our study and the genetic study potentially exists, the genetic study is not yet funded and may not go forward.

Table 2. Postnatal and Genetic Covariates Evaluated as Potential Confounders of Oxygen and Wheezing

Covariates in Home Environment and Exposures The initial questionnaire and 6 month interviews will gather information on other *inhaled exposures* (tobacco, wood stoves, cold air), *residence* (urban vs. rural residence), *infectious exposures* (RSV, palivizumab) and medical risk factors (gastroesophageal reflux, congenital anatomic airway abnormalities)

Covariates in Family History Questionnaires will elicit *family history* of atopy (family history of asthma, eczema or allergy to foods, pets, molds, pollen or dust).

Data Collection: Ascertainment of Primary Exposure

Oxygen Exposure. In the SUPPORT Trial, it is assumed that managing infants with higher vs. lower targeted oxygen saturation range will result in different levels of supplemental oxygen exposure. Because oxygen is the primary exposure in the SUPPORT Follow-on Study and plays a central role in the disease model proposed, oxygen exposure will be quantified carefully. To document the difference in oxygen exposure between groups, FIO2 values will be recorded and analyzed as described in the SUPPORT Trial.

G.5 Sample size estimate with some statistical support based upon primary outcome

The SUPPORT Trial anticipates enrollment of 1506 patients < 28 weeks' gestation, providing 80% power to detect a 10% difference between treatment groups in the incidence of death/CLD and death/stage III Retinopathy of Prematurity (ROP). Assuming mortality of 35% for infants < 1000 grams (NICHD 2002 data), 978 infants would be expected to survive and be eligible for the SUPPORT follow-on study.

Power for detecting a difference between the high vs. low saturation groups for the primary outcome, recurrent wheezing We expect the prevalence of wheezing to be about 0.17 in the low saturation group, and about 0.31 in the high saturation group(12). For the power calculations, we also consider a scenario with a smaller difference between groups: 0.19 for the low saturation group and 0.29 for the high saturation group. We expect the follow up rate to be about 75%, which would result in data on about 733 patients. We also consider a lower follow up rate of 65%, which would result in about 635 patients. Power to detect a difference between groups based on a chi-square test with type I error alpha set at 0.05 is given in Table 7 for each scenario. From those results, we expect to have more than 80% power for the primary outcome. Also of interest are subgroup analyses, where we look separately at the CLD and non-CLD subjects. Of survivors, we expect 37% or 362 infants to have CLD. For the CLD group, we expect the prevalence of wheezing to be about 0.5 in the high saturation group and 0.3 in the low saturation group. If there is a 75% follow up rate, we will have 92% power to detect a difference between the two groups. For the non-CLD subgroup, we expect the prevalence to be 0.2 and 0.1 in the high and low groups, respectively. With 75% follow up, we will have 85% power. Thus, we expect to have adequate power for the primary outcome even in the analyses stratified by CLD.

Table 3. Power for primary outcome, recurrent wheezing.

Follow up rate	Low Saturation	High Saturation	power
75%	0.17	0.31	0.99
75%	0.19	0.29	0.88
65%	0.17	0.31	0.98
65%	0.19	0.29	0.84

We expect the study to be adequately powered for analysis of important secondary outcomes such as use of pulmonary medications. Based on results reported in Davis et al. for infants less than 27 weeks' gestational age [22], we expect the prevalence rate of pulmonary medications to be 0.42 in the high saturation group, and 0.19 in the lower saturation group. In that case, even with a 65% follow up rate, we would have more than 99% power to detect a difference between the groups with a chi-square test. Similarly, the CLD subgroup analyses would have more than 80% power under those assumptions. Based on the power numbers above, we could potentially enroll fewer subjects in the trial and still have adequate power. However, we choose to over enroll slightly to make up for the fact that some patients will likely be lost to follow up.

Data Analysis.
Analysis of primary dichotomous outcomes will be performed by chi square test and presented as a relative risk for development of that outcome. Number of outpatient pulmonary visits for respiratory illnesses will be presented as median values. The Wilcoxon Rank Sum test, a non-parametric alternative to the two-sample t-test, will be used to test for differences between the two groups. Statistical analyses will need to consider the effect of multiple comparison groups on the level of statistical significance. All analyses will be performed in conjunction with the Research Triangle Institute (RTI, North Carolina), the biostatistical support group for the NICHD Neonatal Network. Data will be presented as shown in tables 4-5. Mean FIO2 values in the high and low SpO2 groups will be compared by two sample t-test. Secondary analyses will be done to evaluate the effect of ventilator strategy on pulmonary outcome and presented similarly to table 4 and 5.

Table 4. ***Primary Dichotomous Outcomes***	**Low Saturation**	**High Saturation**	**RR**	**CI**	**p-value**
Parental Report of Recurrent Wheezing (%)					
Physician Diagnosed Recurrent Wheezing (%)					
Need for Outpatient Pulmonary Medications (%)					
Need for Physician Visit for Respiratory Illness (%)					
Need for Re-hospitalization for Respiratory Illness (%)					

Table 5. ***Primary Outcomes – Continuous Outcomes***	**Low Saturation**	**High Saturation**	**p-value**
Number of Physician Visit for Respiratory Illness (Median)			
Number of Emergency Visits for Respiratory Illness (Median)			
Number of Re-hospitalization for Respiratory Illness (Median)			

Expected Results We predict that premature infants managed with a lower targeted oxygen saturation range compared to those managed with a higher targeted oxygen saturation are exposed to lower levels of supplemental oxygen and have reduced risk of recurrent wheezing in the first 18-22 months' CA.

Anticipated Problems and Solutions

1) Participant attrition. As seen in the sample size calculation, the potential for patients to be lost to follow up over time will be offset by over enrolling patients to participate in the follow up. Because patients who enroll in the SUPPORT Trial are randomized, there should be no systematic bias favoring one group over another among patients who are lost to follow up. However, if loss to follow up is in part caused by the treatment or outcomes, this could bias the results. We will therefore investigate whether there are differences in key variables for subjects who are lost to follow up compared to those who remain in the study. For example, we will test whether subjects in one treatment arm were more likely to be lost to follow up than in the other arm. Similarly, we will compare wheezing rates at 6 months' for those who are later lost to follow up compared to those who remain in the study. We do not expect to see any major differences.
2) Low office respiratory health questionnaire response rate. For primary care offices that do not respond to the first mailing, a repeat questionnaire will be mailed. A phone call to the office will be made if there is no response to the second mailing. A $25 honorarium will also be offered to encourage replies.

3) The SUPPORT Follow-on Study of Pulmonary Outcomes has been prepared as the central project for Dr. Stevens' Patient Oriented Clinical Research Grant (K23 Award), submitted 10/1/04. If approved, funds from the K23 will be available to offset a portion of the cost of conducting this SUPPORT Trial Follow-on study. In the event that the K23 is not funded, I will seek additional funding from alternative sources including The American Lung Association and The March of Dimes Foundation.

G.6 Available population/compatibility with other ongoing protocols

Another secondary study proposed by a group independent from ours is looking at the genetics of reactive airways disease in patients enrolled in the SUPPORT Trial. The follow on study proposed here should be complementary to the genetics study, enhancing the both the quality and quantity of data on the prevalence of wheezing and need for outpatient pulmonary care in patients enrolled in the SUPPORT Trial.

G.7 Estimate of projected recruitment time

The recruitment time will be that of the SUPPORT Trial with a 18-22 month period of follow up to ascertain primary and secondary outcomes.

H. RISKS/BENEFITS, WITH ESTIMATE OF FREQUENCY/SEVERITY OF RISKS.

By using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care may be quantified, allowing assessment of whether infants who develop CLD and those who do not have improved pulmonary health as a result of the study intervention. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the follow up visit. We anticipate no risk to the patient of this observational follow on study.

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Center Costs **One Time Costs per Center**	**Hours**	**Cost/center ($43/hour)**	**# Centers**	**Rochester Costs $25/hr***	**Capitation/pt**	**Patients**	**NICHD Network Centers** Portion of Total Cost 1st year**	**NICHD Network Centers** Portion of Total Cost 4 years**	**Rochester** Portion of Total Cost 1st year**	**Rochester** Portion of Total Cost 4 years**	**Total Cost of the Entire Study**
RSRB	5	$215	16				$3,440				$3,440
Annual Costs Per Center											
RSRB renewal	2	$86	16					$1,376			$1,376
SubTotal (Direct Center Costs)							**$3,440**	**$1,376**			$4,816
Capitation Costs											
Cost per Infant											
Capitation											
Interview 1 - Conducted by coordinators at NICHD centers prior to discharge	0.5	$43			$22	700		$15,050		$0	$15,050
Interview 2 - Telephone interview from Rochester	2			$25	$50	700		$15,000		$20,000	$35,000
Interview 3 - Telephone interview from Rochester	2			$25	$50	700		$15,000		$20,000	$35,000
Interview 4 - Telephone interview from Rochester	2			$25	$50	700		$15,000		$20,000	$35,000
Telephone Charges (Long distance charges)										$2,000	$2,000
SubTotal Directs (Interviews)								**$60,050**		**$62,000**	$122,050
Outpatient Office Chart Review				$25		700		$17,500		$0	$17,500
Postage								$0		$500	$500
SubTotal Directs (Chart Reviews)								**$17,500**		**$500**	$18,000
Sub Total Directs (Yearly Interval)							**$3,440**	**$78,926**		**$62,500**	$144,866
Grand Total Directs (Network and Rochester)								***$82,366***		***$62,500***	***$144,866***

*assumes 35,000/year with 29% benefits, working 2000 hours per year

Legend

** Total costs shared between NICHD and Rochester (assuming Dr. Stevens' K23 Patient Oriented Research award is funded, submitted 10/1/04)

^^ Total cost borne by NICHD Neonatal Research Network (if Dr. Stevens' K23 Award is not funded)

Budget Justification

Principal Investigator

Dr. Timothy P. Stevens, MD
Assistant Professor of Pediatrics
Dr. Stevens is a junior investigator. Using the SUPPORT Follow-on Pulmonary Outcome Study described here, Dr. Stevens submitted a Patient Oriented Clinical Research (K23) Grant application to the NICHD on 10/1/04. If funded, a portion of the funds from this K23 award (approximately $62,500) will be used to offset the SUPPORT Trial Pulmonary Outcome Follow-on Study (no salary requested for Dr. Stevens).

Co-Investigators

Dale Phelps, MD, Professor of Pediatrics, Center PI of the NICHD Neonatal Network in Rochester, NY will serve as a co-mentor for Dr. Stevens' K23 award. She will provide specific mentorship in clinical research study design and implementation. Dr. Phelps has extensive experience multi-center trials, including longitudinal follow up of infants enrolled in multi-centered trials. As the NICHD Neonatal Research Network Site Principal Investigator, she will act as a liaison and advocate for Dr. Stevens in the NICHD Neonatal Network (no salary requested).

Peter Szilagyi, MD, MPH, Professor of Pediatrics, Division Chief, General Pediatrics, University of Rochester, will provide senior mentorship of Dr. Stevens' K23 research projects as well his didactic coursework and training in clinical research during the period of the K23 award. He will supervise the clinical research projects. Dr. Szilagyi has distinguished himself in health services research and health outcomes and as a mentor for other clinical researchers. Dr. Szilagyi is the 2002 recipient of the Ambulatory Pediatric Association's Lifetime Research Award, the single highest research honor among general academic pediatricians (no salary requested).

Jonathan Klein, MD, MPH, Associate Professor of Pediatrics and of Community and Preventive Medicine, Director, Health Services Research Group will serve as a co-mentor. Dr. Klein is one of the leading child and adolescent health services researchers in the US. His experience in adolescent medicine and health services research includes studies on adolescent reproductive health care, adolescents' access to care and preferences for care, implementation of preventive services, and studies on the reliability and validity of adolescent report of health behavior and health service use. Dr. Klein is a member of the US Preventive Services Task Force, and is Chair of the American Academy of Pediatrics Committee on Adolescence. Dr. Klein will supervise and mentor Dr. Stevens in the fieldwork necessary to complete this study, including implementation of the telephone follow-up surveys, follow-up design, and data preparation (no salary requested).

Consultants

Neil Finer, MD, Professor of Pediatrics, Vice-Chair of Pediatrics, University of Cal San Diego will serve as a consultant to the SUPPORT Trial Follow On Study that is presented in Specific Aim 1 of this proposal. As National PI for the SUPPORT Trial, Dr. Finer will oversee the primary randomized trial. He will consult on design, implementation, and analysis of the SUPPORT Follow-on Study (no salary requested).

Technical Staff

Caryn Graff-Haven, MPH, MBA, Project Manager, HSR Group. Ms. Graff-Haven is a Senior Health Project Coordinator at the University of Rochester. She will help design and manage development of survey protocols, data entry and cleaning, coordinate and oversee all data acquisition and management activities, and maintain communication between collaborating sites and U of R investigators and staff. Support requested as part of the hourly rate on the budget page.

TBN, Information Analyst. A full time information analyst will be hired to conduct interviews and data entry for the numerous interviews proposed for this project. This will allow for maximal continuity between interviewers and subjects, and will promote adherence to follow-up protocols. Support requested as part of the hourly rate on the budget page.

Student research assistants. Part time student research assistants will conduct interviews and assist with data entry, in particular during the peak enrollment/follow-up time. Support requested as part of the hourly rate on the budget page.

Supplies

General Supplies

$1,200/year is requested each year for supplies, telephone and fax costs, and for photocopying of materials for project meetings.

Other Expenses

Research Subject Review Board Costs – A total of $4,816 is requested to fund a separate informed consent for the follow-on study.

$2,000 is requested for long distance telephone charges to conduct the telephone surveys from Rochester

$17,500 is requested for honoraria to pediatric office staff to complete outpatient chart review.

$500 is requested for stationary, envelopes and postage for mailing outpatient chart review honoraria.

SUPPORT FOLLOW-ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED AT TIME OF ENROLLMENT
PRIOR TO NICU DISCHARGE

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

QUESTIONNAIRE: ENROLLED CHILD
(Nurse Administered)

Child's Name: _____ Date: ____/____/____
Mo. Day Yr.

Child's Sex 1. Male 2. Female

Child's Birthdate ____/____/____ Apgar ____/____
Mo. Day Yr.

Person being interviewed:

1. Child's Mother
2. Child's Father
3. Both Parents
4. Child's female guardian
5. Child's male guardian
6. Other woman (SPECIFY RELATIONSHIP) _____
7. Other man (SPECIFY RELATIONSHIP) _____

1. At this time, we would like a little information about the environment in which your new child will grow up. First, how many people live with you in your home?

Total household members: _____

2a. After the first few months, will your child be sharing a room with other family members on a regular basis?

1. Yes
2. No

2b. IF YES: How many people will sleep in the same room with him/her? _____

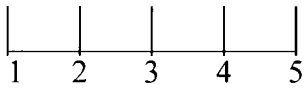
2c. How many living areas are there in your house, excluding closets and bathrooms?_____

3. How many pets are there in the household, either kept inside or out? (RECORD THE NUMBER OF EACH LIVING IN AND OUT OF THE HOUSE).

	Number Kept Inside	Number Kept Outside
Dogs	_____	_____

Cats	_____	_____
Gerbils, Hamsters and Guinea Pigs	_____	_____
Other (Please specify type)		
_____	_____	_____
_____	_____	_____

4. On a scale of 1 to 5, where 1 is not dusty and 5 is very dusty, how dusty would you say your home is compared to other homes in your neighborhood? (CIRCLE APPROPRIATE NUMBER).



Not at all Dusty — Very Dusty

5. Does your home or apartment have air conditioning or some kind of cooling?
   1. Air Conditioning
   2. Evaporative Cooling
   3. Both
   4. None
   5. Other _____
   6. Don't Know

6. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).
   1. Steam or hot water (radiator)
   2. Central gas furnace (furnace)
   3. Electric
   4. Wood Stove
   5. Other
   6. Don't know

7. What fuel is used most for cooking in your home?
   1. Electricity
   2. Gas
   3. Fuel Oil
   4. Wood Stove
   5. Other
   6. Don't Know

8a. Is your child being breast fed? 1. Yes 2. No...SKIP TO QUESTION 9

IF YES,

b. Will this be supplemented with formula? 1. Yes 2. No

c. When do you think the supplement will begin? _____months

d. Do not know when supplements will begin. 1. Yes 2. No

9. Does the mother plan to work outside the home within the next year?
   1. Yes
   2. No
   3. Don't Know

10a. Will your child be cared for by anyone who is not an immediate family member for a major part of the next year?
   1. Yes
   2. No
   3. Maybe

IF YES or MAYBE to 10a:

b. Where will this care be provided?
   1. The parent or guardian's home?
   2. Home of a relative or private sitter?
   3. Day care setting (non-private) ?
   4. Don't Know

c. Will this involve other children, not counting the child's brothers and sisters?
   1. Yes
   2. No

12. Finally, which relative is most likely to have your address in case we lose contact with you?

_____ _____
Name Relationship

_____
Address

_____

SUPPORT FOLLOW ON STUDY

FAMILY HISTORY / FAMILY CONTACT QUESTIONNAIRE - ADMINISTERED PRIOR TO NICU DISCHARGE

1. Name:				
2. Relationship to enrolled child:	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact
3. Age (in years):	________	________	________	________
4. Sex:	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female
5. Does this person currently have:	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
a. Bronchitis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
b. Emphysema?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
c. Bronchiectasis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
d. Asthma?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
e. Inhaled Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
f. Food Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
g. Any other chronic respiratory disease? (SPECIFY)	________ ________	________ ________	________ ________	________ ________
6. How often does this person smoke in the house?	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently

SUPPORT FOLLOW ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED BY TELEPHONE AT 6 AND 12 MONTHS CORRECTED AGE

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Before we begin this interview it would be helpful if you could gather any medications your child has been prescribed or has been taking and have them in front of you. Can you do that now or is there a better time to call you?

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing concerns your child may have.

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

4a. Has his/her chest ever sounded wheezy or whistling?
   3. Yes
   4. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?

1	2	3	4	5
Very rarely				On Most days

e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing ~

g. Has this child's wheezing/whistling occurred as attacks?
   1. Yes
   2. No

h. Has this child ever been awakened at night by wheeze or by shortness of breath?
   1. Yes
   2. No

i. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

j. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES. BE SURE TO COMPLETE QUESTIONS 24 AND 25

5. Does this child's chest sound wheezy or whistling during or shortly after vigorous exercise or crying?
   1. Yes, usually
   2. Yes, occasionally
   3. No

6a. Has he/she ever had episodes of shortness of breath or chest tightness?
   1. Yes
   2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6A:

b. Has this ever occurred when the child is at rest?
   1. Yes
   2. No

c. During the past year, how many episodes did he/she have?

1 2 3 4 5
Few — Very many

d. How old was this child when he/she had the first such episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

OR: check here if the child still has condition: ~

f. Has the child's chest ever sounded wheezy or whistling during episodes of shortness of breath or chest tightness?
   1. Yes
   2. No

g. Has he/she ever seen a doctor for shortness of breath or chest tightness?
   1. Yes
   2. No

h. Has this child ever taken any medicine for shortness of breath?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

7. Has this child ever had a cough when he/she did not have a cold?
   1. Yes
   2. No . . . SKIP TO QUESTION 6

IF **YES** TO QUESTION 5a

b. At what time of the day has this cough usually occurred? (CIRCLE ALL THAT APPLY) 1.
   1. In the morning, shortly after rising
   2. Later in the day
   3. During the night
   4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?
   1. Yes
   2. No

d. How often has this child been bothered by coughing?

1	2	3	4	5
Very Rarely				On most days

e. How old was the child when he/she first began to cough?
   _____ months

   OR: check here if child is still coughing: _

f. How old was this child when he/she stopped coughing?
   _____ months

g. Has the cough usually been dry or loose?
   1. Dry
   2. Loose

h. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?
   1. Yes
   2. No

i. How often has your child raised phlegm, sputum or mucus when coughing?
   1. Never
   2. Occasionally
   3. Often

j. Has he/she ever seen a doctor about the cough?
   1. Yes
   2. No

Does this child cough during or shortly after vigorous exercise?
   1. Yes, usually
   2. Yes, occasionally
   3. No

8a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 9a

IF **YES** TO QUESTION 8A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: ~

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ months

OR: check here if doctor never said he/she had asthma: ~

e. **During the past year**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past year**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

9a. Has your child ever had bronchitis?

1. Yes
2. No . . . SKIP TO QUESTION 10a

IF **YES** TO QUESTION 9a:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last episode occurred?

_____ months

OR: check here if child still has bronchitis ___

d. How old was this child when you were first told by a doctor that he/she had bronchitis?

_____ months

OR: check here if doctor never said he/she had bronchitis___

e. How often has this child had bronchitis?

1. one episode only
2. 2-3 episodes
3. 4 or more separate episodes
4. almost constantly

f. During the past year, how much trouble did he/she have with bronchitis?

1 2 3 4 5

None A great deal

g. During the past year, did this child take any medicine for bronchitis?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 254

10a. Has your child ever had croup?

1. Yes
2. No . . . SKIP TO QUESTION 11a

IF **YES** TO QUESTION 10a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of croup?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

11a. Has your child ever had bronchiolitis, or any wheezing illness in the first year of life not due to asthma?

1. Yes
2. No . . . SKIP TO QUESTION 12a

IF **YES** TO QUESTION 11A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

12a. Has your child **ever** had pneumonia?

1. Yes
2. No . . . SKIP TO QUESTION 13

IF **YES** TO QUESTION 12a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

13a. Was this child breast fed?

1. Yes
2. No . . . SKIP TO QUESTION 14

IF **YES** TO QUESTION 13a:

b. For how many months was this child breast fed?

1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

14a. Has the mother smoked at all since this child was born?

1. Yes
2. No . . . SKIP TO QUESTION 15a

IF **YES** TO QUESTION 14a:

b. For how many months did the mother smoke since this child was born?

_____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES)

_____ cigarettes
_____ pipes
_____cigars
_____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?

Never
Occasionally
Frequently

15a. Has the father smoked at all since the child was born?

1. Yes
2. No . . . SKIP TO QUESTION 16

IF **YES** TO QUESTION 15a:

b. For how many months did the father smoke since this child's birth?

_____ months

c. On the average, how many of each of the following did he smoke per day during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES).

_____ cigarettes
_____ pipes
_____ cigars
_____ non-tobacco cigarettes

d. How often has the father smoked in the same room with this child?

1. Never
2. Occasionally
3. Frequently

16. Did any other household member regularly smoke in the house since this child's birth?

1. Yes
2. No

17. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

18. How many brothers and sisters (including half siblings) does this child have?

_____

19a. Are there any other children living in your household **besides** this child and all of his/her siblings?

1. Yes
2. No . . . SKIP TO QUESTION 20

IF **YES** TO QUESTION 19a:

b. How many children other than this child and his/her siblings live in your house?

_____

20. Do you have any pets?

1. Yes
2. No

1❑ Dogs #:_____
2❑ Cats #: _____
3❑ Other #:_____

21. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).

1. steam or hot water
2. central gas furnace
3. wall or floor gas furnace
4. electric
5. other
6. don't know

OUTPATIENT RESPIRATORY PROPHYLAXIS

22. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?

1. Yes
2. No

23. Did this child receive a flu shot?

1. Yes
2. No

OUTPATIENT RESPIRATORY SUPPORT

24a. Is your child on any oxygen therapy (oxygen tank at home)?

1. Yes
2. No

IF **YES** TO QUESTION 24a:

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

*lpm = liters per minute

25. Is your child taking any medicines for asthma or wheezing?

1. Yes
2. No
3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as:* ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other _____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

THANK YOU FOR YOUR COOPERATION

SUPPORT FOLLOW ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED AT 18-22 MONTH FOLLOW UP VISIT

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing concerns your child may have.

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

4a. Has his/her chest ever sounded wheezy or whistling?
   1. Yes
   2. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?

1	2	3	4	5
Very rarely				On Most days

e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing _

g. Has this child's wheezing/whistling occurred as attacks?
   1. Yes
   2. No

h. Has this child ever been awakened at night by wheeze or by shortness of breath?
   1. Yes
   2. No

i. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

j. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

5. Does this child's chest sound wheezy or whistling during or shortly after vigorous exercise or crying?
   1. Yes, usually
   2. Yes, occasionally
   3. No

6a. Has he/she ever had episodes of shortness of breath or chest tightness?
   1. Yes
   2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6A:

b. Has this ever occurred when the child is at rest?
   1. Yes
   2. No

c. During the past year, how many episodes did he/she have?

1	2	3	4	5
Few				Very many

d. How old was this child when he/she had the first such episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

OR: check here if the child still has condition: _

f. Has the child's chest ever sounded wheezy or whistling during episodes of shortness of breath or chest tightness?
   1. Yes
   2. No

g. Has he/she ever seen a doctor for shortness of breath or chest tightness?
   1. Yes
   2. No

h. Has this child ever taken any medicine for shortness of breath?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

7. Has this child ever had a cough when he/she did not have a cold?
   1. Yes
   2. No . . . SKIP TO QUESTION 6

IF **YES** TO QUESTION 5a

b. At what time of the day has this cough usually occurred? (CIRCLE ALL THAT APPLY)
   1.
   1. In the morning, shortly after rising
   2. Later in the day
   3. During the night
   4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?
   1. Yes
   2. No

d. How often has this child been bothered by coughing?

1	2	3	4	5
Very Rarely				On most days

e. How old was the child when he/she first began to cough?
   ____ months

   OR: check here if child is still coughing: _

f. How old was this child when he/she stopped coughing?
   _____ months

g. Has the cough usually been dry or loose?
   1. Dry
   2. Loose

h. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?
   1. Yes
   2. No

i. How often has your child raised phlegm, sputum or mucus when coughing?
   1. Never
   2. Occasionally
   3. Often

j. Has he/she ever seen a doctor about the cough?
   1. Yes
   2. No

Does this child cough during or shortly after vigorous exercise?
   1. Yes, usually
   2. Yes, occasionally
   3. No

8a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 9a

IF **YES** TO QUESTION 8A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: _

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ _ months

OR: check here if doctor never said he/she had asthma: _

e. **During the past year**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past year**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

9a. Has your child ever had bronchitis?

1. Yes
2. No . . . SKIP TO QUESTION 10a

IF **YES** TO QUESTION 9a:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last episode occurred?

_____ months

OR: check here if child still has bronchitis ___

d. How old was this child when you were first told by a doctor that he/she had bronchitis?

_____ months

OR: check here if doctor never said he/she had bronchitis___

e. How often has this child had bronchitis?

1. one episode only
2. 2-3 episodes
3. 4 or more separate episodes
4. almost constantly

f. During the past year, how much trouble did he/she have with bronchitis?

1 2 3 4 5

None A great deal

g. During the past year, did this child take any medicine for bronchitis?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 254

10a. Has your child ever had croup?

1. Yes
2. No . . . SKIP TO QUESTION 11a

IF **YES** TO QUESTION 10a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of croup?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

11a. Has your child ever had bronchiolitis, or any wheezing illness in the first year of life not due to asthma?

1. Yes
2. No . . . SKIP TO QUESTION 12a

IF **YES** TO QUESTION 11A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

12a. Has your child **ever** had pneumonia?

1. Yes
2. No . . . SKIP TO QUESTION 13

IF **YES** TO QUESTION 12a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

13a. Was this child breast fed?

1. Yes
2. No . . . SKIP TO QUESTION 14

IF **YES** TO QUESTION 13a:

b. For how many months was this child breast fed?

1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

14a. Has the mother smoked at all since this child was born?

1. Yes
2. No . . . SKIP TO QUESTION 15a

IF **YES** TO QUESTION 14a:

b. For how many months did the mother smoke since this child was born?

_____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES)

_____ cigarettes
_____ pipes
_____cigars
_____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?

Never
Occasionally
Frequently

15a. Has the father smoked at all since the child was born?

1. Yes
2. No . . . SKIP TO QUESTION 16

IF **YES** TO QUESTION 15a:

b. For how many months did the father smoke since this child's birth?

_____ months

c. On the average, how many of each of the following did he smoke per day during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES).

_____ cigarettes
_____ pipes
_____ cigars
_____ non-tobacco cigarettes

d. How often has the father smoked in the same room with this child?

1. Never
2. Occasionally
3. Frequently

16. Did any other household member regularly smoke in the house since this child's birth?

1. Yes
2. No

17. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

18. How many brothers and sisters (including half siblings) does this child have?

_____

19a. Are there any other children living in your household **besides** this child and all of his/her siblings?

1. Yes
2. No . . . SKIP TO QUESTION 20

IF **YES** TO QUESTION 19a:

b. How many children other than this child and his/her siblings live in your house?

_____

20. Do you have any pets?

1. Yes
2. No

1❑ Dogs #:_____
2❑ Cats #: _____
3❑ Other #:_____

21. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).

1. steam or hot water
2. central gas furnace
3. wall or floor gas furnace
4. electric
5. other
6. don't know

OUTPATIENT RESPIRATORY PROPHYLAXIS

22. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?

1. Yes
2. No

23. Did this child receive a flu shot?

1. Yes
2. No

OUTPATIENT RESPIRATORY SUPPORT

24a. Was your child ever on any oxygen therapy (oxygen tank at home)?

1. Yes
2. No

IF **YES** TO QUESTION 24a:

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

*lpm = liters per minute

25. Is your child taking any medicines for asthma or wheezing?

1. Yes
2. No
3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as*: ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other _____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

ATOPY HISTORY

26. **During the past year**, for how many days has this child been unable to do his/her usual activities because of illnesses such as chest (not head) colds, bronchitis, asthma or pneumonia?

_____ days

27. How many head colds (common colds) **per year** does this child usually have?

1. Few (0-3 per year)
2. Some (4-5 per year)
3. Frequent (6-9 per year)
4. Constant (more than 9 per year)

28a. Has your child **ever** had hay fever or any other condition that makes his/her nose runny, stuffy, or itchy **apart** from colds?

1. Yes
2. No . . . SKIP TO QUESTION 29

IF **YES** TO QUESTION 28a:

b. How old was your child when you first noticed this condition?

_____ months

c. How old was this child when he/she stopped having this condition?

_____ months

OR: check here if child still has condition ~

d. When this child has the runny or stuffy nose, does he/she also usually:

Cough?	1. Yes 2. No
Wheeze?	1. Yes 2. No
Have shortness of breath?	1. Yes 2. No

29. Has this child **ever** had allergies which cause nose, eye or lung problems?

1. Yes
2. No

30. Has a doctor **ever** told you that this child had sinus trouble?

1. Yes
2. No

31a. Has this child **ever** been allergic to any food?

1. Yes
2. No

b. Has he/she **ever** been allergic to any medicine?

1. Yes
2. No

32a. Has this child **ever** had eczema (allergic skin rash)?

1. Yes

2. No . . . SKIP TO QUESTION 33a

IF **YES** TO QUESTION 32A:

b. Has a doctor told you this child had eczema?
1. Yes
2. No

c. At what age did the eczema begin?
_____ months

d. How old was this child when he/she last had eczema?
_____ months

OR: check here if child still has eczema ~

33a. Was this child breast fed?
1. Yes
2. No . . . SKIP TO QUESTION 34

IF **YES** TO QUESTION 33a:

b. For how many months was this child breast fed?
1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

34. At what age was formula introduced?
1. Never
2. less than 1 month
3. 1-3 months
4. 4-6 months
5. more than 6 months

35. At what age was cow's milk (nonformula) started?
1. Never
2. Less than 1 month
3. 1-3 months
4. 4-6 months
5. 7-9 months
6. 9-11 months
7. 12 or more months

36. At what age did he/she begin to receive table foods?
1. less than 1 month
2. 1-3 months
3. 4-6 months
4. 7-9 months
5. more than 9 months

THANK YOU FOR YOUR COOPERATION

From: Lemons, James A
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Secondary
Date: Monday, January 31, 2005 2:00:03 PM

I am pretty sure we already voted yes. Thanks

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 28, 2005 2:24 PM
To: Barbara Stoll (barbara_stoll@oz.ped.emory.edu); Charles Rosenfeld (crosen@mednet.swmed.edu); Jon Tyson (Jon.E.Tyson@uth.tmc.edu); Michele Walsh (mcw3@po.cwru.edu); Shahnaz Duara (sduara@miami.edu); Seetha Shankaran (s_shankaran@wayne.edu); David Stevenson (dstevenson@stanford.edu); Lemons, James A
Subject: FW: SUPPORT Secondary

HI, I am missing several votes on this SUPPORT secondary. Please send your vote ASAP.
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD)
Sent: Friday, January 07, 2005 3:00 PM
To: 'Abbot Laptook (E-mail)'; 'Abhik Das'; 'Carlo Waldemar (E-mail)'; 'Charles Rosenfeld'; 'Dale Phelps'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; 'Jobe Alan (E-mail)'; 'Lemons Jim (E-mail)'; 'Michael O'Shea'; 'Michelle Walsh'; 'Neil Finer'; 'Oh William (E-mail)'; 'Poole Kenneth (E-mail)'; 'Ronald GOldberg'; 'Shahnaz Duara'; 'Shankaran Seetha (E-mail)'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; 'Walid Salhab'
Cc: 'petrie@rti.org'
Subject: SUPPORT Secondary

Hi,
Attached is a secondary study to SUPPORT For Pulmonary Follow Up. Please review this and send me a vote by January 24, 2005 for moving this forward to an ultimate financial/budget vote (You will be asked to vote on the budget items prior to next year's capitation awards).
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: David Stevenson
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: SUPPORT Secondary
Date: Monday, January 31, 2005 10:36:29 AM

Rose,

Yes.
David

At 11:24 AM 1/28/2005, you wrote:

> HI, I am missing several votes on this SUPPORT secondary. Please send your vote ASAP.
> Thanks
> Rose
>
> ---
>
> **From:** Higgins, Rosemary (NIH/NICHD)
> **Sent:** Friday, January 07, 2005 3:00 PM
> **To:** 'Abbot Laptook (E-mail)'; 'Abhik Das'; 'Carlo Waldemar (E-mail)'; 'Charles Rosenfeld'; 'Dale Phelps'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; 'Jobe Alan (E-mail)'; 'Lemons Jim (E-mail)'; 'Michael O'Shea'; 'Michelle Walsh'; 'Neil Finer'; 'Oh William (E-mail)'; 'Poole Kenneth (E-mail)'; 'Ronald GOldberg'; 'Shahnaz Duara'; 'Shankaran Seetha (E-mail)'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; 'Walid Salhab'
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> higginsr@mail.nih.gov

From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Secondary
Date: Monday, January 31, 2005 9:32:11 AM

Rose
okay with me
Seetha

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 28, 2005 2:24 PM
To: Barbara Stoll (barbara_stoll@oz.ped.emory.edu); Charles Rosenfeld (crosen@mednet.swmed.edu); Jon Tyson (Jon.E.Tyson@uth.tmc.edu); Michele Walsh (mcw3@po.cwru.edu); Shahnaz Duara (sduara@miami.edu); Seetha Shankaran (s_shankaran@wayne.edu); David Stevenson (dstevenson@stanford.edu); Jim Lemons (jlemons@iupui.edu)
Subject: FW: SUPPORT Secondary

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From:	Higgins, Rosemary (NIH/NICHD)
To:	Stoll, Barbara J; Charles Rosenfeld (Charles.Rosenfeld@UTSouthwestern.edu); Jon.E.Tyson@uth.tmc.edu; Michele Walsh (Michele.walsh@cwru.edu); sduara@miami.edu; Seetha Shankaran ; dstevenson@stanford.edu; jlemons@iupui.edu
Subject:	FW: SUPPORT Secondary
Date:	Friday, January 28, 2005 2:24:00 PM
Attachments:	SUPPORT Follow-on Study 10-1 (2).doc Costs for Follow-on.xls Budget Justification.doc Appendix A.doc Appendix B.doc Appendix C.doc

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Thanks
Rose

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Sent: Friday, January 07, 2005 3:00 PM
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NICHD SUPPORT Trial Follow-on Study of Outpatient Pulmonary Outcomes

University of Rochester
Golisano Children's Hospital at Strong

Timothy P. Stevens, MD
Peter Szilagyi, MD, MPH
Dale Phelps, MD

Proposal Updated: October 1, 2004

Contact Information:

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A. ABSTRACT

Statement of Problem Premature infants have a greater risk for wheezing and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor for later wheezing, the etiology of recurrent wheezing in formerly premature infants is not known.

Hypotheses The goal of the clinical project detailed here is to understand better the antecedents of recurrent wheezing among preterm infants during early childhood by evaluating the effect of treatment with different levels of targeted oxygen saturation in the immediate neonatal period. **The overarching hypothesis is that premature infants exposed to supplemental oxygen suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater symptomatic airway dysfunction when challenged with subsequent environmental or infectious exposures.**

Hypothesis #1- Relative to infants managed with a higher SpO2 range, infants who are managed with a lower targeted SpO2 range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' corrected age (CA) whether they develop CLD or not.

Hypothesis #2- Relative to infants managed with prophylactic surfactant and conventional ventilation, infants who are managed with the early use of CPAP and a permissive ventilator strategy will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' CA whether they develop CLD or not.

Design

Longitudinal follow-up of infants enrolled in the SUPPORT Trial to determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the prevalence of recurrent wheezing and volume of outpatient pulmonary care in the first 18 months' CA.

Definition of outcomes:

A) Parental Report of Wheezing
B) Physician Diagnosed Wheezing.
C) Volume of Outpatient Pulmonary Care including number of pulmonary medications, office and emergency room visits and re-hospitalizations for respiratory illnesses.

Ascertainment of outcomes:

Outcomes will be measured at 4 time points in the first 18-22 months' CA as follows:

1. NICU discharge -baseline interview at to obtain family and environmental history
2. Six months' CA - telephone interview to ascertain prevalence of wheezing and obtain interval history of need for pulmonary care.
3. Twelve months' CA - telephone interview as at 6 months'
4. 18-22 months' CA- Prior to NICHD follow-up clinic visit, a telephone interview to ascertain prevalence of wheezing and obtain interval history of need for pulmonary care will be administered and primary care physician contact information collected for outpatient office chart review.
5. Outpatient chart review- data extraction from patient outpatient medical record.

Anticipated Results

We anticipate that, for infants who develop CLD and those who do not, treatment with a lower vs. higher targeted oxygen saturation range will result in less frequent episodes of wheezing and less need for outpatient pulmonary care in the first 18-22 months' CA.

Benefits and Risks

The proposed SUPPORT Follow-on Pulmonary Outcome Study will directly measure symptomatic airway dysfunction and outpatient pulmonary morbidity in infants treated with either a higher vs. lower targeted oxygen saturation. These data will provide important insight into the effect of different levels of supplemental oxygen exposure on airway growth and development in formerly premature infants. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the neurodevelopmental follow up visit. We anticipate no risk to the patient of this observational follow-on study.

B. STATEMENT OF THE PROBLEM

Premature infants have a greater risk for wheezing and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor for later symptomatic airway dysfunction, the etiology of recurrent wheezing in formerly premature infants is not known.

C. HYPOTHESES

The overarching hypothesis is that premature infants exposed to supplemental oxygen and, to a lesser extent, mechanical ventilation, in the neonatal period suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction and respiratory symptoms when challenged with subsequent environmental or infectious exposures.

Specific Hypotheses:

Hypothesis #1- We hypothesize that relative to infants managed with a higher SpO2 range, infants managed with a lower SpO2 range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care at 18-22 months' CA.

Hypothesis #2- We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

Hypothesis #3- We hypothesize that **among infants with CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

Hypothesis #4- We hypothesize that **among infants without CLD**, infants managed with early use of CPAP and permissive ventilator strategy relative to infants managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

D. SPECIFIC AIMS

The goal of this project is to understand better the etiology of recurrent wheezing among formerly premature infants during early childhood by examining the interaction of oxygen exposure (targeted SpO2 range), surfactant therapy and early nasal CPAP in the newborn period.

SA#1 - Measure the effect of lower vs. higher targeted SpO2 on the prevalence of recurrent wheezing and volume of outpatient pulmonary care among infants born $24^{0/7}$ - $27^{6/7}$ weeks' gestation during the first 18-22 months' CA.

SA#2 - Measure the effect of early CPAP and permissive ventilator strategy compared with prophylactic surfactant and traditional ventilator strategy on the prevalence of recurrent wheezing and volume of outpatient pulmonary care among infants born 24-27 weeks' gestation during the first 18-22 months' CA.

SA#3 – Among infants who develop CLD, determine whether CLD is milder in infants managed with low compared with high targeted SpO2 by measuring recurrent wheezing and volume of outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

SA#4 – Among infants who do not develop CLD, determine whether pulmonary outcome is better for infants managed with a low compared with high targeted SpO2 range by measuring the prevalence of recurrent wheezing and need for outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory

strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

E. RATIONALE/JUSTIFICATION

Although synergy in producing airway injury may exist between oxygen toxicity and mechanical forces applied to the lung, animal and human data suggest that exposure to high concentrations of supplemental oxygen alone is sufficient to cause airway narrowing and greater reactivity to subsequent challenges. Understanding the relative contributions of oxygen toxicity and mechanical forces on airway growth and development may facilitate development of targeted therapies for preventing or reducing symptomatic airway dysfunction in premature infants.

Why measure recurrent wheezing and outpatient pulmonary care as an outcome from a clinical NICU interventional trial?

1) Important information will be available on the effect of oxidant gas exposure on airway development and later symptomatic airway dysfunction. Exposure to oxidant gas has been causally linked with later wheezing. Existing data on the relationship between supplemental oxygen therapy and wheezing come from longitudinal cohort studies, a design that suffers from intrinsic limitations that make controlling for potential confounders of respiratory outcome difficult. By randomizing infants to higher vs. lower target saturation ranges, and thereby presumably higher or lower concentrations of inspired oxygen, *the SUPPORT Trial creates a unique, and perhaps the only, opportunity to evaluate the effect of different levels of supplemental oxygen on subsequent symptomatic airway dysfunction and need for outpatient pulmonary care after NICU discharge.*

2) Using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care can be directly quantified, allowing assessment of whether infants both with and without CLD have improved pulmonary health as a result of the study intervention.

3) The incidence of CLD, defined as an oxygen requirement at 36 weeks' PMA, is an incomplete measure of pulmonary outcome in formerly premature infants during early infancy. CLD as defined above reflects alveolar gas diffusion and NICU oxygen needs. However, outpatient pulmonary morbidity for formerly premature infants is often airway related, involving wheezing either as a primary symptom such as bronchiolitis or as a complicating symptom of lower respiratory tract infection such as pneumonia. The studies proposed here will directly measure the effect of a randomized NICU-based clinical intervention on symptomatic airway dysfunction and outpatient pulmonary morbidity.

4) The risk of a negative trial is reduced. Because the diagnosis of CLD does not completely predict need for outpatient pulmonary care, clinically significant improvements in pulmonary morbidity may occur with minimal or no change in the incidence of CLD. This result has occurred in other interventional trials in which no difference in CLD were observed (12).

5) At present, there is no standard way to measure symptomatic airway dysfunction in premature infants in NICHD pulmonary intervention trials. There is need for a better measure to assess clinical pulmonary outcome to recognize and promote therapies that reduce need for outpatient care of former extremely premature infants.

6) By measuring outpatient pulmonary outcomes, the cost-effectiveness of the SUPPORT study interventions can be assessed. It is reasonable to expect that the SUPPORT Trial interventions will improve outpatient pulmonary outcomes for infants who ultimately develop CLD as well as those who do not. This proposed follow-on study collects the primary data necessary to quantify the cost-effectiveness of this therapy.

F. BACKGROUND / PREVIOUS STUDIES

Recurrent Wheezing In Preterm Infants is a Significant Public Health Problem

Outpatient pulmonary morbidity, especially recurrent wheezing and need for outpatient pulmonary care, is an understudied but clinically important outcome measure for former premature infants with and without CLD. Infants born weighing < 1500 grams (very low birth weight, VLBW) and especially infants born weighing < 1000 grams are at increased risk for small airway narrowing, airway hyperreactivity, wheezing, and nighttime cough (1-11). Up to 30-40% of formerly extremely premature infants have episodes of wheezing after NICU discharge with many requiring bronchodilators and frequent health care visits. Up to 40-50% of premature infants require re-hospitalization, mostly for treatment of respiratory illnesses (9;12;13). In analysis of cross sectional data from the National Maternal Infant Health Survey and 1991 Longitudinal Follow up Survey, the prevalence of asthma-like recurrent wheezing varied markedly with birth weight. Infants with normal birth weight (NBW, > 2500 grams) had a 6.7% prevalence of asthma compared to 10.9% of low birth weight infants (LBW, 1500-2499 grams) and 21.9% for VLBW (14). Mean per capital asthma related costs have been estimated to be 5 times greater for VLBW compared with NBW infants. The net effect is that VLBW infants, who comprise 2% of asthma patients, consume up to 7% of asthma-related therapy costs (14).

Animal Studies

Animal studies suggest that exposure of the premature lung to hyperoxia (without concomitant mechanical ventilation) for relatively brief periods is sufficient to cause airway remodeling and smooth muscle changes that predispose toward airway narrowing and hyperreactivity to subsequent environmental challenges (15-18). In a rhesus monkey model of asthma, Schlegle et al. exposed infant monkeys to repeated cycles of inhaled House Dust Mite Allergen (HDMA), ozone or filtered air. While repeated exposure to either ozone or HDMA had mild effects, exposure to cycles of ozone followed by HDMA resulted in asthma like changes with significant increases in serum IgE, serum histamine, peripheral eosinophilia and greater airway reactivity. Using supplemental oxygen rather than the stronger oxidant ozone, Schulman et al. found that exposure of newborn guinea pigs to 70% oxygen for 96 hours resulted in airway hyperreactivity at 2 and 9 days after the cessation of oxygen. In cell models, intracellular glutathione buffers airway cells against oxidant injury during hyperoxia (19;20). Although the critical period for lung development is comparatively brief in laboratory animals compared with human infants, the duration of hyperoxic exposure (and risk of oxygen toxicity) for treatment of neonatal lung disease may extend for much longer periods in premature infants known to be deficient in anti-oxidant systems such as intracellular glutathione.

Premature Infants <u>With CLD</u> Are At Greatest Risk For Recurrent Wheezing

Among premature infants, infants with bronchopulmonary dysplasia (BPD) are at highest risk for poor pulmonary outcome after NICU discharge. Infants with CLD have small airway compromise with decreased forced expiratory flow velocities, airway hyperreactivity, and increased functional residual volume suggesting airway obstruction (2;5;9;21-24). In a pulmonary follow up of infants with HMD or BPD, De Klein et al. found infants with BPD had reduced FEV1 at baseline while infants with RDS but not BPD had significant improvements in FEV1 following bronchodilator therapy. In this study, a history of recurrent wheezing predicted abnormal pulmonary function (25). In a recent study of infants with CLD, Robin et al. found that 50% of infants with CLD had symptoms of recurrent wheezing and 35% showed significant airway responsiveness to bronchodilators, evidenced by a 24% increase in forced expiratory flow velocity at 75% of expired forced vital capacity (FEF_{75}). This study demonstrated the relationship between recurrent wheezing as a clinical symptom and the physiologic measurement of airway obstruction. Infants with CLD and a history of recurrent wheezing showed greater expiratory flow limitation, hyperinflation, and airway responsiveness to albuterol compared to those without a history of recurrent wheezing (24).

Premature Infants Without CLD Have Significant Airway Dysfunction

Among VLBW infants who do not develop CLD, several studies of pulmonary outcome have found an association between neonatal oxygen exposure and increased prevalence of expiratory flow dysfunction and airway hyperreactivity (4;11;26-29). Some authors attribute reductions in airway function to intrinsically small airways as a consequence of poor intrauterine growth rather than superimposed airway injury or reactivity from neonatal respiratory disease (1;30). However, because small airways alone do not fully explain findings of airway hyperreactivity, other mechanisms of small airway dysfunction are necessary to explain respiratory symptoms.

Several pulmonary outcome studies have reported significant increases (2-fold or more) in airway obstruction among VLBW infants without CLD following exposure to as little as an FIO2 of 0.4 for 5 days (3;4;8;26). Not all studies have had similar results suggesting variability in effect or susceptibility of babies to oxygen exposure (31;32). In 1982, Coates et al. described increased small airway resistance at 10 year follow up of mildly premature infants (mean gestational age 31 weeks and birth weight 2000 grams) treated with a high oxygen (O2) regimen and those exposed to a low O2 regimen for the treatment of respiratory distress syndrome (RDS). Mechanical ventilation was not used in either group. Pulmonary function tests were performed on survivors receiving either the low or high supplemental oxygen regimen ten years after their initial illness. Infants treated with high levels of supplemental oxygen alone (no mechanical ventilation) had decrements in airway function similar to decrements in function reported for a historical cohort of RDS survivors treated with ventilation and high levels of supplemental oxygen. From these data, the authors concluded that neonatal exposure to high oxygen concentrations in the absence of mechanical ventilation is capable of causing long-term change in small airways (28). These studies suggest that use of lower supplemental oxygen concentration may improve respiratory health of infants who do not develop CLD.

Premature Infants Without CLD Have Increased Risk of Recurrent Wheezing and Need for Outpatient Pulmonary Care.

For VLBW infants without CLD, the prevalence of parental or physician reported wheezing is increased compared with term infants, with estimates of the prevalence of wheezing ranging from 10-38% (4;8). Prevalence of wheezing requiring medications is greater compared with term infants. VLBW infants have a 2-4-fold increase in respiratory related re-hospitalization rates compared with term infants (4;8;33-35). Although most studies have found the risk of recurrent wheezing remains elevated throughout childhood, an Australian longitudinal follow-up cohort of VLBW infants found the prevalence of wheezing remained elevated for 2 years then returned to baseline (32;36).

Prevalence of Symptomatic Airway Dysfunction in Formerly Preterm Infants During the Surfactant Era Remains High

With the advent of surfactant therapy, survival for small infants increased dramatically and the incidence of CLD changed minimally (37-40). Classic BPD evolved into the new CLD characterized by reduced alveolarization and more variable airway changes (41). Pulmonary follow up studies during the surfactant era showed reduced pulmonary morbidity in surfactant treated patients. Typical of these studies, Sell et al. found the incidence of asthma was significantly lower in infants given synthetic surfactant compared with those given air placebo. Pelkonen et al. performed PFT measurements on 40 children aged 7-12 years who were born before 30 weeks of gestation with an immature surfactant system, and were randomized to one of three treatment groups: prophylactic surfactant, rescue surfactant and placebo (air). Spirometric parameters of preterm born children were compared with those of 20 children born at term. Bronchial obstruction was found in 53% of the prophylactically treated group, in 36% of the rescue group, in 67% of the placebo group, and in 0% of the control group (42). A recent report suggests that the introduction of surfactant therapy markedly altered the pulmonary outcome of premature infants. Published in 2001, the Newborn Lung Function Project Group reported results of a prospective 12-year follow-up of VLBW infants following the introduction of surfactant therapy. Among infants with CLD, wheezing symptoms decreased from 50 to 16% from the period before compared with the period after surfactant therapy became available. However, among infants without CLD the prevalence of wheezing increased from 14% to 38% with the introduction of surfactant. These data suggest that surfactant therapy has an effect on outpatient respiratory health and underscores the need to

consider outpatient pulmonary outcomes in evaluating therapeutic strategies that potentially decrease surfactant replacement therapy.

CLD is an Incomplete Predictor of Outpatient Pulmonary Morbidity

Several authors have looked to respiratory symptoms and need for outpatient pulmonary care as outcome measures for neonatal lung disease (9;10;12;24). In 1988, from a retrospective chart review of 605 premature infants < 1500 grams, Shennan et al. found that the presence of BPD (oxygen requirement at 36 weeks PMA) had a 63% positive predictive value and a 90% negative predictive value for abnormal pulmonary outcome in the first 2 years of age. However, this study from before the era of exogenous surfactant therapy defined abnormal pulmonary outcome as death, oxygen requirement at 40 weeks PMA, 2 or more respiratory related hospital admissions, wheezing requiring drug therapy or persistent wheezing resulting in growth failure, handicap or hypotonia at 1 year of age. Such restrictive criteria for abnormal pulmonary outcome are likely to underestimate the burden of recurrent wheezing on former premature infants and their families. Several recent interventional studies show that CLD is an incomplete predictor of clinical wheezing and need for outpatient pulmonary care and suggest that differences in oxygen exposure or oxidant stress may affect pulmonary outcome without affecting the incidence of CLD.

Interventional Trials That Did Not Reduce CLD But Did Reduce Outpatient Pulmonary Morbidity.

Recent data in preterm infants treated with human recombinant superoxide dismutase (SOD) found that anti-oxidant therapy did not reduce the incidence of CLD. However, among infants < 27 weeks gestation SOD therapy resulted in significant reductions in the first year after NICU discharge in the number of emergency room visits and number of re-hospitalizations for respiratory problems and reductions in the need for bronchodilators suggesting a reduced prevalence of wheezing in patients treated with SOD (12). In a randomized, multi-center trial from Helsinki, N acetyl cysteine did not reduce the incidence of CLD. Outpatient pulmonary outcome of these patients has not been reported.

Treatment of Premature Infants With Higher Targeted Oxygen Saturations Is Associated with Poorer Pulmonary Outcome

In the STOP-ROP Study, infants exposed to higher levels of oxygen to achieve a targeted saturation of 96-99% compared with 89-94% had greater risk of adverse pulmonary events including pneumonia, chronic lung disease exacerbations and need for diuretics, oxygen and hospitalization at 3 months'' corrected age. *Although all infants in this study had CLD at enrollment, different targeted oxygen saturation were associated with large differences in pulmonary morbidity.* Adverse pulmonary outcomes occurred with differences in FIO2 of as little as 10% for patients treated with ventilation, CPAP or hood (36% $\pm$ 14% vs. 46% $\pm$ 20%, respectively for low vs. high saturation range) and 5% for infants treated with nasal cannula, (26% $\pm$ 6% vs. 31% $\pm$ 11%, respectively for low vs. high saturation range) (44). In a similar study, The Benefits of Oxygen Saturation Targeting (BOOST) Trial randomized infants < 30 weeks' gestation to higher (95-98%) or lower (91-94%) saturations ranges beginning at 32 weeks' PMA to determine whether infants managed with higher targeted saturation range showed better growth and neurodevelopment. As in the STOP-ROP study, need for oxygen therapy was prolonged. Trends towards an increased risk of pulmonary death and fewer outpatient office visits (median 27.5 vs. 31.3, $p < .11$) were seen in the lower targeted oxygen saturation group (13).

G. METHOD/ PROCEDURES

NICHD SUPPORT Trial Follow-on Study of Pulmonary Outcomes

G.1 Description of study design

This study will add an 18-22 month longitudinal, prospective follow-on study of surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial.

G.2 Definition of study population

Infants with gestational age of $24^{0/7}$-$27^{6/7}$ weeks' gestation by best obstetrical estimate.

Inclusion criteria:

- Full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Parents/legal guardians have provided consent for enrollment
- No known major congenital malformations
- Survival to hospital discharge

Exclusion Criteria

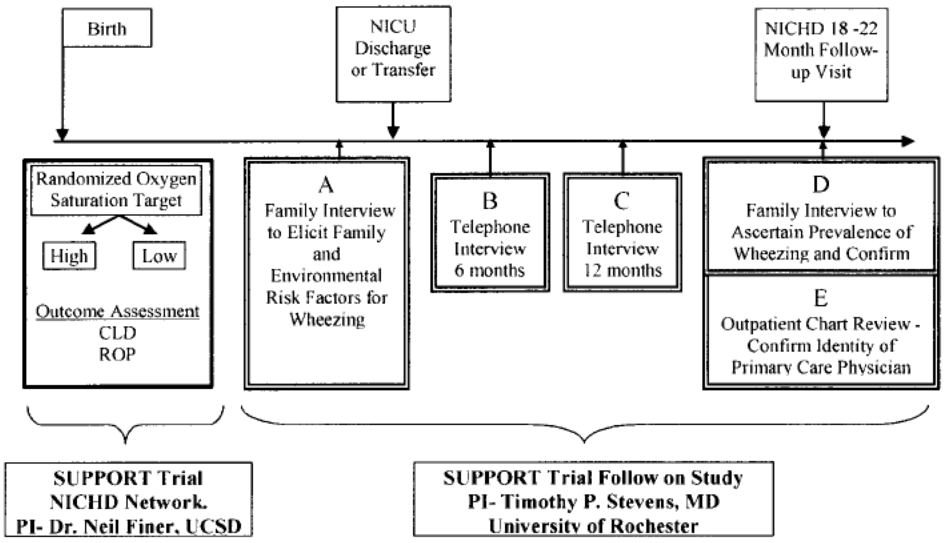
- Transport to the center after delivery
- Parents/legal guardians refuse consent
- Research apparatus/study personnel are not available.
- Gestational age $< 24^{0/7}$ or $\geq 28^{0/7}$ weeks' gestation

G.3 Description of study intervention

Before delivery, infants will be randomized to subsequent management with high vs. low target oxygen saturation according to the SUPPORT Protocol. The SUPPORT Follow-on Study proposed here begins just prior to NICU discharge (Figure 1).

SUPPORT Trial Follow-on Study

Figure 1. **Infants $24^{0/7}$-$27^{6/7}$ Weeks' Gestation**



"A" will be administered at NICHD Network Centers

"B-E" will be conducted long distance by University of Rochester research staff.

Fig 1, A. Parent (Guardian) Interview to Elicit Family and Environmental Risk Factors for Wheezing The family interview will be administered at each participating Network Center by site study nurses prior to NICU discharge or transfer. The questions are based on intake questions used by the Tucson Respiratory Study and are designed to elicit family history of asthma, atopy, and home environment and to identify likely care givers (Questionnaire in Appendix G). Consent for release of medical information will be obtained to facilitate contacting physician offices to obtain office data.

Fig 1, B. Telephone Interview at 6 months' CA – respiratory interval history

Fig 1, C. Telephone Interview at 12 months' CA – respiratory interval history

Telephone interviews will be undertaken at 6 and 12 months' to obtain limited interval history of respiratory problems including wheezing, medications used, and health services sought for respiratory related problems (Questionnaire in Appendix H).

Fig 1, D. Parental Interview to Ascertain Prevalence of Wheezing and Confirm Risk Factors This parent interview will also be administered by telephone, prior to the regularly scheduled 18-22 month NICHD developmental follow up clinic visit (an NICHD funded, ongoing program). Contacting parents prior to the office visit will help improve the Developmental Follow Up Clinic attendance rate and will allow the clinic visit to provide a back up means to contact the family. All telephone interviews, the 2 limited telephone interviews and the second family history interview at 18-22 months', will be conducted long distance from Rochester (see below). The interview questionnaires are based on questionnaires administered by the Tucson Respiratory Study at approximately one year of age (Questionnaire in Appendix I). Questions are designed to ascertain the frequency and severity of wheezing episodes. In addition, risk factors obtained at the 1st interview will be confirmed or updated.

Fig 1, E. Outpatient Chart Review - Confirm Identity of Primary Care Physician

To confirm results of physician report of wheezing obtained by telephone interview, patients undergoing telephone interview will have their primary care physician's medical record reviewed.

E.1 – Physician report of wheezing

E.2 – Frequency of outpatient pulmonary care. The volume of outpatient pulmonary care including outpatient primary care physician office visits, pulmonary specialty care, emergency room visits, hospitalizations and the number and duration of pulmonary medications will be obtained from primary care physician chart review. To help assure compliance by primary care office staff, a $25 honorarium will be offered for successful completion of the chart review form (45-47).

G.4 Precise definition of primary/secondary outcomes

1) Definition Of Parental Report Of Wheezing. The primary outcome will be parental report of recurrent wheezing, defined as more than 1 episode of wheezing, using questions adapted from the Tucson Children's Respiratory Study, questions validated in a large prospective birth cohort study of term infants (48-54) (Appendices G-I). The primary question used in the telephone interview for this project will be the same as the one used in the Tucson Children's Respiratory Study "Did your child have wheezing?" (48) Additional questions will be used to further characterize the wheezing episodes, identify wheezing associated with a viral illness (parental report of a "cold") and wheezing associated with environmental exposures. The prevalence of health services utilization (outpatient office visits for pulmonary care, ER visits, re-hospitalizations, bronchodilator therapy) for pulmonary reasons will also be collected during interviews. The Tucson study also ascertained frequency of office visits and use of respiratory medications. Of full term infants whose parents reported that their infant had an episode of wheezing, 40% had recurrent wheezing in the first 6 years compared with 22% of infants whose parents reported no episodes of wheezing in the first 3 years.

Parental Report of Wheezing Is A Reliable Outcome Measure of Airway Dysfunction

Evaluation of frequency and severity of respiratory symptoms and volume of pulmonary care has been used as the primary outcome in multiple follow up studies of term and premature infants (10;12;14;43). A recent review evaluated the value of respiratory symptom history ascertained by parental questionnaire in determining the risk for developing asthma in early childhood. By evaluating 9 large, longitudinal, full term birth cohort studies and reviewing the original questionnaire from 7 of these studies, Koopman found that the questions posed to parents

eliciting a history of wheezing in their infants were similar. Parental report of wheezing predicted an increased risk for later respiratory symptoms including asthma. In the studies proposed here, recurrent wheezing ascertained by parental report will be used as the primary outcome, rather than physiologic measurements of airway dysfunction, for several reasons (Table 3). Although the goal of using respiratory questionnaires in the studies proposed here is to measure pulmonary outcome, not to predict asthma, studies of asthma questionnaires and their ability to predict asthma demonstrates the validity of parental report of wheezing as an accurate measure of airway dysfunction.

Reasons to Use Parental Report of Wheezing as Primary Outcome Measure

- Parental interview can be performed more readily on large numbers of patients. The validity of this approach has been shown in several longitudinal studies including The Tucson Respiratory Study, upon which the interview questions are based.
- Recurrent wheezing is highly correlated with changes on pulmonary function testing. In a study of infants with CLD, a history of recurrent wheezing was associated with greater expiratory flow limitation, hyperinflation and airway responsiveness to albuterol on pulmonary function testing compared to those without a history of recurrent wheezing (24).
- Parental recall of respiratory illnesses has been shown to correlate strongly with review of medical office records. For asthma and bronchitis in the past year, Pless et al. found good agreement between recall of 288 parents and physician office chart review. Parental education and occupation were not predictive of a parent's ability to recall the illness (55). In an assessment of parental recall done to evaluate minor injury in children, Harel found recall declined with time, with the best recall occurring in the first 3 months' after injury with further decline after 6 months' from the time of the injury (47;56;57).

Advantages of Conducting Telephone Interviews From a Single Center

Conducting the telephone interviews from Rochester will:

1) require less effort from the individual Network Centers (Network Centers may assist in tracking families)
2) allow standardization of the telephone interview by a core group of trained interviewers
3) blind the telephone interviewer to the SUPPORT Trial study group designation
4) reduce the cost of the study by consolidating the telephone training and follow up at one site.

2) Definition Of Physician Diagnosed Wheezing. A secondary outcome will be physician report of recurrent wheezing, defined as more than 1 episode of wheezing. Physician diagnosed wheezing will be collected by parental report during telephone interviews using the question "Did a doctor tell you your child had wheezing?" and "Where did you see that Doctor, primary care, emergency room, hospital or other?" In addition, review of the primary care physician medical chart will be undertaken to identify episodes of physician documented wheezing.

3) Definitions of Secondary Outcomes - Measures of Volume of Outpatient Pulmonary Care

Important secondary outcomes of outpatient pulmonary morbidity will be collected (Table 1).

Table 1. ***Secondary Outcomes, Covariates and Sources***	
Outcomes	**Source**
Secondary Outcomes	
Number and duration of outpatient pulmonary medications including bronchodilator, diuretic, methylxanthine, and inhaled and systemic steroid therapy.	Family interview, primary care chart review
Number of office visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of emergency room visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of re-hospitalizations for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Growth at 18 months' CA (height, weight and head circumference)	NICHD follow up clinic data

Data Collection: Ascertainment of Outcomes - Field Work

Ascertainment of Wheezing and Outpatient Pulmonary Morbidity By Telephone Interview.
There will be 4 parental interviews over 18-22 months', one prior to NICU discharge and 3 subsequent telephone interviews at 6 month intervals to collect data on the prevalence of recurrent wheezing, need for outpatient pulmonary care, and relevant environmental and family history covariates (Figure 1, A-D above). Based on review of longitudinal studies of full term infants in which follow up patient contacts occurred quarterly to once every 18 months', a 6 month interval for follow up patient contacts is planned in an effort to reduce parental recall omissions which are more likely to occur with less frequent follow up (43;56). The 4 interviews are designed to collect the primary and secondary outcomes of the follow-on study. Other inpatient and outpatient data will be collected as part of the NICHD Neonatal Research Network Generic Database (GDB) and Follow-up Program.

The University of Rochester Neonatology Research Group has conducted similar telephone interview designs as part of an ophthalmologic outcome study of patients enrolled in a randomized trial of cryotherapy to treat ROP and a 15-year, longitudinal neurological assessment conducted by telephone survey among 132 infants treated with surfactant. Telephone follow up rates were 96% follow up at 7 years and 95% follow up at 15 years (58). In the study proposed here, the University of Rochester Health Services Research Group (HSR Group), will conduct the telephone interviews.

In telephone follow up surveys conducted by the HSR Group, follow up rates at 12 months' have exceed 75% in populations at high risk for being lost to follow up (59-65). The Rochester HSR Group has over 2,500 square feet of newly renovated space. Under the direction of Drs. Jonathan Klein and Peter Szilagyi, the HSR group includes sufficient space and all appropriate equipment and personnel to perform telephone interviews and database management for the project presented here. The HSR Group will conduct 3 telephone interviews from Rochester. Drs. Peter Szilagyi and Jonathan Klein, co-directors of the HSR Group, are mentors for Dr. Stevens' K23 Patient Oriented Research Award application. Drs. Klein and Szilagyi will work with Dr. Stevens and Dr. Phelps in the implementation and management of the tracking and respiratory questionnaire program. To facilitate tracking and record keeping, Dr. Stevens will design and write a database to track enrolled patients and their contact information, next scheduled interview, and record answers to phone interview questions. Each interview will close with a question as to whether the family plans a new address or phone number prior to the next interview. The names and phone number of a friend or relative and their primary care physician will be sought so that they may be contacted in the event that contact with the patient is lost. By interviewing families every 6 months', a higher follow up rate will be achieved because family contact information will not become so out of date that the family is lost or that re-contacting them is inefficient. We anticipate that each interview will require 2 hours of staff time, with 20-30 minutes to conduct the interview and 90 minutes to contact family and enter data.

Interview Instruments – (Appendices A-C) Questionnaires based on the Tucson Children's Respiratory Study, a well validated questionnaire used in a large longitudinal cohort study that followed healthy full term infants from birth to over 20 years of age. The questionnaires have been updated to reflect currently available respiratory medications and modified to address the health issues that are faced by formerly premature infants such as use of palivizumab for RSV prophylaxis. In addition, the questionnaires are designed to elicit a thorough history of possible covariates, such as environmental and infectious exposures and family histories of atopy, asthma or respiratory disease.

Physician Office Records Assessment of Wheezing and Outpatient Pulmonary Morbidity Physician office charts will be reviewed to determine physical findings of wheezing, medication use and respiratory related hospitalization history. For primary care pediatricians, the family's consent authorizing release of medical information and an office contact questionnaire will be mailed or faxed to the provider. The questionnaire will be based on a similar document used by the Rochester Research Group to obtain medical information on respiratory issues. To help assure compliance with completing the questionnaire, a $25 honorarium will be offered to the office staff.

Data Collection: Ascertainment of Environmental and Genetic Covariates

Ascertainment of important environmental exposures and genetic risk factors that might confound the relationship between supplemental oxygen exposure and recurrent wheezing will be obtained along with the primary outcome during the same telephone and family interviews (Table 2). A second follow-on study to the SUPPORT Trial, not affiliated with the studies proposed here, is being independently proposed by other investigators to study specific genetic markers that predict greater risk of CLD. Although synergy between our study and the genetic study potentially exists, the genetic study is not yet funded and may not go forward.

Table 2. Postnatal and Genetic Covariates Evaluated as Potential Confounders of Oxygen and Wheezing

Covariates in Home Environment and Exposures The initial questionnaire and 6 month interviews will gather information on other *inhaled exposures* (tobacco, wood stoves, cold air), *residence* (urban vs. rural residence), *infectious exposures* (RSV, palivizumab) and medical risk factors (gastroesophageal reflux, congenital anatomic airway abnormalities)

Covariates in Family History Questionnaires will elicit *family history* of atopy (family history of asthma, eczema or allergy to foods, pets, molds, pollen or dust).

Data Collection: Ascertainment of Primary Exposure

Oxygen Exposure. In the SUPPORT Trial, it is assumed that managing infants with higher vs. lower targeted oxygen saturation range will result in different levels of supplemental oxygen exposure. Because oxygen is the primary exposure in the SUPPORT Follow-on Study and plays a central role in the disease model proposed, oxygen exposure will be quantified carefully. To document the difference in oxygen exposure between groups, FIO2 values will be recorded and analyzed as described in the SUPPORT Trial.

G.5 Sample size estimate with some statistical support based upon primary outcome

The SUPPORT Trial anticipates enrollment of 1506 patients < 28 weeks' gestation, providing 80% power to detect a 10% difference between treatment groups in the incidence of death/CLD and death/stage III Retinopathy of Prematurity (ROP). Assuming mortality of 35% for infants < 1000 grams (NICHD 2002 data), 978 infants would be expected to survive and be eligible for the SUPPORT follow-on study.

Power for detecting a difference between the high vs. low saturation groups for the primary outcome, recurrent wheezing We expect the prevalence of wheezing to be about 0.17 in the low saturation group, and about 0.31 in the high saturation group(12). For the power calculations, we also consider a scenario with a smaller difference between groups: 0.19 for the low saturation group and 0.29 for the high saturation group. We expect the follow up rate to be about 75%, which would result in data on about 733 patients. We also consider a lower follow up rate of 65%, which would result in about 635 patients. Power to detect a difference between groups based on a chi-square test with type I error alpha set at 0.05 is given in Table 7 for each scenario. From those results, we expect to have more than 80% power for the primary outcome. Also of interest are subgroup analyses, where we look separately at the CLD and non-CLD subjects. Of survivors, we expect 37% or 362 infants to have CLD. For the CLD group, we expect the prevalence of wheezing to be about 0.5 in the high saturation group and 0.3 in the low saturation group. If there is a 75% follow up rate, we will have 92% power to detect a difference between the two groups. For the non-CLD subgroup, we expect the prevalence to be 0.2 and 0.1 in the high and low groups, respectively. With 75% follow up, we will have 85% power. Thus, we expect to have adequate power for the primary outcome even in the analyses stratified by CLD.

Table 3. Power for primary outcome, recurrent wheezing.

Follow up rate	Low Saturation	High Saturation	power
75%	0.17	0.31	0.99
75%	0.19	0.29	0.88
65%	0.17	0.31	0.98
65%	0.19	0.29	0.84

We expect the study to be adequately powered for analysis of important secondary outcomes such as use of pulmonary medications. Based on results reported in Davis et al. for infants less than 27 weeks' gestational age [22], we expect the prevalence rate of pulmonary medications to be 0.42 in the high saturation group, and 0.19 in the lower saturation group. In that case, even with a 65% follow up rate, we would have more than 99% power to detect a difference between the groups with a chi-square test. Similarly, the CLD subgroup analyses would have more than 80% power under those assumptions. Based on the power numbers above, we could potentially enroll fewer subjects in the trial and still have adequate power. However, we choose to over enroll slightly to make up for the fact that some patients will likely be lost to follow up.

Data Analysis.

Analysis of primary dichotomous outcomes will be performed by chi square test and presented as a relative risk for development of that outcome. Number of outpatient pulmonary visits for respiratory illnesses will be presented as median values. The Wilcoxon Rank Sum test, a non-parametric alternative to the two-sample t-test, will be used to test for differences between the two groups. Statistical analyses will need to consider the effect of multiple comparison groups on the level of statistical significance. All analyses will be performed in conjunction with the Research Triangle Institute (RTI, North Carolina), the biostatistical support group for the NICHD Neonatal Network. Data will be presented as shown in tables 4-5. Mean FIO2 values in the high and low SpO2 groups will be compared by two sample t-test. Secondary analyses will be done to evaluate the effect of ventilator strategy on pulmonary outcome and presented similarly to table 4 and 5.

Table 4. ***Primary Dichotomous Outcomes***	**Low Saturation**	**High Saturation**	**RR**	**CI**	**p-value**
Parental Report of Recurrent Wheezing (%)					
Physician Diagnosed Recurrent Wheezing (%)					
Need for Outpatient Pulmonary Medications (%)					
Need for Physician Visit for Respiratory Illness (%)					
Need for Re-hospitalization for Respiratory Illness (%)					

Table 5. ***Primary Outcomes – Continuous Outcomes***	**Low Saturation**	**High Saturation**	**p-value**
Number of Physician Visit for Respiratory Illness (Median)			
Number of Emergency Visits for Respiratory Illness (Median)			
Number of Re-hospitalization for Respiratory Illness (Median)			

Expected Results We predict that premature infants managed with a lower targeted oxygen saturation range compared to those managed with a higher targeted oxygen saturation are exposed to lower levels of supplemental oxygen and have reduced risk of recurrent wheezing in the first 18-22 months' CA.

Anticipated Problems and Solutions

1) Participant attrition. As seen in the sample size calculation, the potential for patients to be lost to follow up over time will be offset by over enrolling patients to participate in the follow up. Because patients who enroll in the SUPPORT Trial are randomized, there should be no systematic bias favoring one group over another among patients who are lost to follow up. However, if loss to follow up is in part caused by the treatment or outcomes, this could bias the results. We will therefore investigate whether there are differences in key variables for subjects who are lost to follow up compared to those who remain in the study. For example, we will test whether subjects in one treatment arm were more likely to be lost to follow up than in the other arm. Similarly, we will compare wheezing rates at 6 months' for those who are later lost to follow up compared to those who remain in the study. We do not expect to see any major differences.
2) Low office respiratory health questionnaire response rate. For primary care offices that do not respond to the first mailing, a repeat questionnaire will be mailed. A phone call to the office will be made if there is no response to the second mailing. A $25 honorarium will also be offered to encourage replies.

3) The SUPPORT Follow-on Study of Pulmonary Outcomes has been prepared as the central project for Dr. Stevens' Patient Oriented Clinical Research Grant (K23 Award), submitted 10/1/04. If approved, funds from the K23 will be available to offset a portion of the cost of conducting this SUPPORT Trial Follow-on study. In the event that the K23 is not funded, I will seek additional funding from alternative sources including The American Lung Association and The March of Dimes Foundation.

G.6 Available population/compatibility with other ongoing protocols

Another secondary study proposed by a group independent from ours is looking at the genetics of reactive airways disease in patients enrolled in the SUPPORT Trial. The follow on study proposed here should be complementary to the genetics study, enhancing the both the quality and quantity of data on the prevalence of wheezing and need for outpatient pulmonary care in patients enrolled in the SUPPORT Trial.

G.7 Estimate of projected recruitment time

The recruitment time will be that of the SUPPORT Trial with a 18-22 month period of follow up to ascertain primary and secondary outcomes.

H. RISKS/BENEFITS, WITH ESTIMATE OF FREQUENCY/SEVERITY OF RISKS.

By using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care may be quantified, allowing assessment of whether infants who develop CLD and those who do not have improved pulmonary health as a result of the study intervention. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the follow up visit. We anticipate no risk to the patient of this observational follow on study.

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Center Costs **One Time Costs per Center**	Hours	Cost/center ($43/hour)	# Centers	Rochester Costs $25/hr*	Capitation/pt	Patients	NICHD Network Centers** Portion of Total Cost 1st year	NICHD Network Centers** Portion of Total Cost 4 years	Rochester** Portion of Total Cost 1st year	Rochester** Portion of Total Cost 4 years	**Total Cost for the Entire Study^^**
RSRB	5	$215	16				$3,440				**$3,440**
Annual Costs Per Center											
RSRB renewal	2	$86	16					$1,376			**$1,376**
SubTotal (Direct Center Costs)							**$3,440**	**$1,376**			**$4,816**
Capitation Costs											
Cost per Infant											
Capitation											
Interview 1 - Conducted by coordinators at NICHD centers prior to discharge	0.5	$43			$22	700		$15,050		$0	**$15,050**
Interview 2 - Telephone interview from Rochester	2			$25	$50	700		$15,000		$20,000	**$35,000**
Interview 3 - Telephone interview from Rochester	2			$25	$50	700		$15,000		$20,000	**$35,000**
Interview 4 - Telephone interview from Rochester	2			$25	$50	700		$15,000		$20,000	**$35,000**
Telephone Charges (Long distance charges)										$2,000	**$2,000**
SubTotal Directs (Interviews)								**$60,050**		**$62,000**	**$122,050**
Outpatient Office Chart Review				$25		700		$17,500		$0	**$17,500**
Postage								$0		$500	**$500**
SubTotal Directs (Chart Reviews)								**$17,500**		**$500**	**$18,000**
Sub Total Directs (Yearly Interval)							**$3,440**	**$78,926**		**$62,500**	**$144,866**
Grand Total Directs (Network and Rochester)								***$82,366***		***$62,500***	***$144,866***

*assumes 35,000/year with 29% benefits, working 2000 hours per year

Legend

** Total costs shared between NICHD and Rochester (assuming Dr. Stevens' K23 Patient Oriented Research award is funded, submitted 10/1/04)

^^ **Total cost born by NICHD Neonatal Research Network (if Dr. Stevens' K23 Award is not funded)**

Budget Justification

Principal Investigator

Dr. Timothy P. Stevens, MD
Assistant Professor of Pediatrics
Dr. Stevens is a junior investigator. Using the SUPPORT Follow-on Pulmonary Outcome Study described here, Dr. Stevens submitted a Patient Oriented Clinical Research (K23) Grant application to the NICHD on 10/1/04. If funded, a portion of the funds from this K23 award (approximately $62,500) will be used to offset the SUPPORT Trial Pulmonary Outcome Follow-on Study (no salary requested for Dr. Stevens).

Co-Investigators

Dale Phelps, MD, Professor of Pediatrics, Center PI of the NICHD Neonatal Network in Rochester, NY will serve as a co-mentor for Dr. Stevens' K23 award. She will provide specific mentorship in clinical research study design and implementation. Dr. Phelps has extensive experience multi-center trials, including longitudinal follow up of infants enrolled in multi-centered trials. As the NICHD Neonatal Research Network Site Principal Investigator, she will act as a liaison and advocate for Dr. Stevens in the NICHD Neonatal Network (no salary requested).

Peter Szilagyi, MD, MPH, Professor of Pediatrics, Division Chief, General Pediatrics, University of Rochester, will provide senior mentorship of Dr. Stevens' K23 research projects as well his didactic coursework and training in clinical research during the period of the K23 award. He will supervise the clinical research projects. Dr. Szilagyi has distinguished himself in health services research and health outcomes and as a mentor for other clinical researchers. Dr. Szilagyi is the 2002 recipient of the Ambulatory Pediatric Association's Lifetime Research Award, the single highest research honor among general academic pediatricians (no salary requested).

Jonathan Klein, MD, MPH, Associate Professor of Pediatrics and of Community and Preventive Medicine, Director, Health Services Research Group will serve as a co-mentor. Dr. Klein is one of the leading child and adolescent health services researchers in the US. His experience in adolescent medicine and health services research includes studies on adolescent reproductive health care, adolescents' access to care and preferences for care, implementation of preventive services, and studies on the reliability and validity of adolescent report of health behavior and health service use. Dr. Klein is a member of the US Preventive Services Task Force, and is Chair of the American Academy of Pediatrics Committee on Adolescence. Dr. Klein will supervise and mentor Dr. Stevens in the fieldwork necessary to complete this study, including implementation of the telephone follow-up surveys, follow-up design, and data preparation (no salary requested).

Consultants

Neil Finer, MD, Professor of Pediatrics, Vice-Chair of Pediatrics, University of Cal San Diego will serve as a consultant to the SUPPORT Trial Follow On Study that is presented in Specific Aim 1 of this proposal. As National PI for the SUPPORT Trial, Dr. Finer will oversee the primary randomized trial. He will consult on design, implementation, and analysis of the SUPPORT Follow-on Study (no salary requested).

Technical Staff

Caryn Graff-Haven, MPH, MBA, Project Manager, HSR Group. Ms. Graff-Haven is a Senior Health Project Coordinator at the University of Rochester. She will help design and manage development of survey protocols, data entry and cleaning, coordinate and oversee all data acquisition and management activities, and maintain communication between collaborating sites and U of R investigators and staff. Support requested as part of the hourly rate on the budget page.

TBN, Information Analyst. A full time information analyst will be hired to conduct interviews and data entry for the numerous interviews proposed for this project. This will allow for maximal continuity between interviewers and subjects, and will promote adherence to follow-up protocols. Support requested as part of the hourly rate on the budget page.

Student research assistants. Part time student research assistants will conduct interviews and assist with data entry, in particular during the peak enrollment/follow-up time. Support requested as part of the hourly rate on the budget page.

Supplies

General Supplies
$1,200/year is requested each year for supplies, telephone and fax costs, and for photocopying of materials for project meetings.

Other Expenses

Research Subject Review Board Costs – A total of $4,816 is requested to fund a separate informed consent for the follow-on study.

$2,000 is requested for long distance telephone charges to conduct the telephone surveys from Rochester

$17,500 is requested for honoraria to pediatric office staff to complete outpatient chart review.

$500 is requested for stationary, envelopes and postage for mailing outpatient chart review honoraria.

SUPPORT FOLLOW-ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED AT TIME OF ENROLLMENT
PRIOR TO NICU DISCHARGE

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

QUESTIONNAIRE: ENROLLED CHILD
(Nurse Administered)

Child's Name: _____ Date: ____/____/____
Mo. Day Yr.

Child's Sex 1. Male 2. Female

Child's Birthdate ____/____/____ Apgar ____/____
Mo. Day Yr.

Person being interviewed:

1. Child's Mother
2. Child's Father
3. Both Parents
4. Child's female guardian
5. Child's male guardian
6. Other woman (SPECIFY RELATIONSHIP) _____
7. Other man (SPECIFY RELATIONSHIP) _____

1. At this time, we would like a little information about the environment in which your new child will grow up. First, how many people live with you in your home?

Total household members: _____

2a. After the first few months, will your child be sharing a room with other family members on a regular basis?

1. Yes
2. No

2b. IF YES: How many people will sleep in the same room with him/her? _____

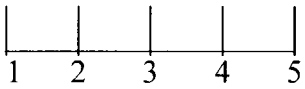
2c. How many living areas are there in your house, excluding closets and bathrooms?_____

3. How many pets are there in the household, either kept inside or out? (RECORD THE NUMBER OF EACH LIVING IN AND OUT OF THE HOUSE).

	Number Kept Inside	Number Kept Outside
Dogs	_____	_____

Cats	_____	_____
Gerbils, Hamsters and Guinea Pigs	_____	_____
Other (Please specify type)		
_____ _____	_____	_____
_____ _____	_____	_____

4. On a scale of 1 to 5, where 1 is not dusty and 5 is very dusty, how dusty would you say your home is compared to other homes in your neighborhood? (CIRCLE APPROPRIATE NUMBER).



Not at all Dusty — Very Dusty

5. Does your home or apartment have air conditioning or some kind of cooling?
   1. Air Conditioning
   2. Evaporative Cooling
   3. Both
   4. None
   5. Other _____
   6. Don't Know

6. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).
   1. Steam or hot water (radiator)
   2. Central gas furnace (furnace)
   3. Electric
   4. Wood Stove
   5. Other
   6. Don't know

7. What fuel is used most for cooking in your home?
   1. Electricity
   2. Gas
   3. Fuel Oil
   4. Wood Stove
   5. Other
   6. Don't Know

8a. Is your child being breast fed? 1. Yes 2. No...SKIP TO QUESTION 9

IF YES,

b. Will this be supplemented with formula? 1. Yes 2. No

c. When do you think the supplement will begin? _____months

d. Do not know when supplements will begin. 1. Yes 2. No

9. Does the mother plan to work outside the home within the next year?
   1. Yes
   2. No
   3. Don't Know

10a. Will your child be cared for by anyone who is not an immediate family member for a major part of the next year?
   1. Yes
   2. No
   3. Maybe

IF YES or MAYBE to 10a:

b. Where will this care be provided?
   1. The parent or guardian's home?
   2. Home of a relative or private sitter?
   3. Day care setting (non-private) ?
   4. Don't Know

c. Will this involve other children, not counting the child's brothers and sisters?
   1. Yes
   2. No

12. Finally, which relative is most likely to have your address in case we lose contact with you?

_____ _____
Name Relationship

_____
Address

_____

SUPPORT FOLLOW ON STUDY

FAMILY HISTORY / FAMILY CONTACT QUESTIONNAIRE - ADMINISTERED PRIOR TO NICU DISCHARGE

1. Name:				
2. Relationship to enrolled child:	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact
3. Age (in years):	________	________	________	________
4. Sex:	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female
5. Does this person currently have:	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
a. Bronchitis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
b. Emphysema?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
c. Bronchiectasis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
d. Asthma?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
e. Inhaled Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
f. Food Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
g. Any other chronic respiratory disease? (SPECIFY)	________ ________	________ ________	________ ________	________ ________
6. How often does this person smoke in the house?	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently

SUPPORT FOLLOW ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED BY TELEPHONE AT 6 AND 12 MONTHS CORRECTED AGE

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Before we begin this interview it would be helpful if you could gather any medications your child has been prescribed or has been taking and have them in front of you. Can you do that now or is there a better time to call you?

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing concerns your child may have.

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

4a. Has his/her chest ever sounded wheezy or whistling?
   3. Yes
   4. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?

1	2	3	4	5
Very rarely				On Most days

e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing ~

g. Has this child's wheezing/whistling occurred as attacks?
   1. Yes
   2. No

h. Has this child ever been awakened at night by wheeze or by shortness of breath?
   1. Yes
   2. No

i. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

j. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES. BE SURE TO COMPLETE QUESTIONS 24 AND 25

5. Does this child's chest sound wheezy or whistling during or shortly after vigorous exercise or crying?
   1. Yes, usually
   2. Yes, occasionally
   3. No

6a. Has he/she ever had episodes of shortness of breath or chest tightness?
   1. Yes
   2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6A:

b. Has this ever occurred when the child is at rest?
   1. Yes
   2. No

c. During the past year, how many episodes did he/she have?

1 2 3 4 5
Few Very many

d. How old was this child when he/she had the first such episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

OR: check here if the child still has condition: ~

f. Has the child's chest ever sounded wheezy or whistling during episodes of shortness of breath or chest tightness?
   1. Yes
   2. No

g. Has he/she ever seen a doctor for shortness of breath or chest tightness?
   1. Yes
   2. No

h. Has this child ever taken any medicine for shortness of breath?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

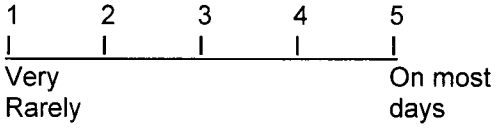
7. Has this child ever had a cough when he/she did not have a cold?
   1. Yes
   2. No . . . SKIP TO QUESTION 6

IF **YES** TO QUESTION 5a

b. At what time of the day has this cough usually occurred? (CIRCLE ALL THAT APPLY) 1.
   1. In the morning, shortly after rising
   2. Later in the day
   3. During the night
   4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?
   1. Yes
   2. No

d. How often has this child been bothered by coughing?



e. How old was the child when he/she first began to cough?
   ____ months

   OR: check here if child is still coughing: _

f. How old was this child when he/she stopped coughing?
   _____ months

g. Has the cough usually been dry or loose?
   1. Dry
   2. Loose

h. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?
   1. Yes
   2. No

i. How often has your child raised phlegm, sputum or mucus when coughing?
   1. Never
   2. Occasionally
   3. Often

j. Has he/she ever seen a doctor about the cough?
   1. Yes
   2. No

Does this child cough during or shortly after vigorous exercise?
   1. Yes, usually
   2. Yes, occasionally
   3. No

8a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 9a

IF **YES** TO QUESTION 8A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: ~

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ _ months

OR: check here if doctor never said he/she had asthma: ~

e. **During the past year**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past year**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

9a. Has your child ever had bronchitis?

1. Yes
2. No . . . SKIP TO QUESTION 10a

IF **YES** TO QUESTION 9a:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last episode occurred?

_____ months

OR: check here if child still has bronchitis ___

d. How old was this child when you were first told by a doctor that he/she had bronchitis?

_____ months

OR: check here if doctor never said he/she had bronchitis___

e. How often has this child had bronchitis?

1. one episode only
2. 2-3 episodes
3. 4 or more separate episodes
4. almost constantly

f. During the past year, how much trouble did he/she have with bronchitis?

1 2 3 4 5

None A great deal

g. During the past year, did this child take any medicine for bronchitis?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 254

10a. Has your child ever had croup?

1. Yes
2. No . . . SKIP TO QUESTION 11a

IF **YES** TO QUESTION 10a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of croup?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

11a. Has your child ever had bronchiolitis, or any wheezing illness in the first year of life not due to asthma?

1. Yes
2. No . . . SKIP TO QUESTION 12a

IF **YES** TO QUESTION 11A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

12a. Has your child **ever** had pneumonia?

1. Yes
2. No . . . SKIP TO QUESTION 13

IF **YES** TO QUESTION 12a:

b. Was this diagnosed by a doctor?
1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?
1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

13a. Was this child breast fed?

1. Yes
2. No . . . SKIP TO QUESTION 14

IF **YES** TO QUESTION 13a:

b. For how many months was this child breast fed?
1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

14a. Has the mother smoked at all since this child was born?

1. Yes
2. No . . . SKIP TO QUESTION 15a

IF **YES** TO QUESTION 14a:

b. For how many months did the mother smoke since this child was born?
_____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES)

_____ cigarettes
_____ pipes
_____cigars
_____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?
Never
Occasionally
Frequently

15a. Has the father smoked at all since the child was born?

1. Yes
2. No . . . SKIP TO QUESTION 16

IF **YES** TO QUESTION 15a:

b. For how many months did the father smoke since this child's birth?

_____ months

c. On the average, how many of each of the following did he smoke per day during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES).

_____ cigarettes
_____ pipes
_____ cigars
_____ non-tobacco cigarettes

d. How often has the father smoked in the same room with this child?

1. Never
2. Occasionally
3. Frequently

16. Did any other household member regularly smoke in the house since this child's birth?

1. Yes
2. No

17. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

18. How many brothers and sisters (including half siblings) does this child have?

_____

19a. Are there any other children living in your household **besides** this child and all of his/her siblings?

1. Yes
2. No . . . SKIP TO QUESTION 20

IF **YES** TO QUESTION 19a:

b. How many children other than this child and his/her siblings live in your house?

_____

20. Do you have any pets?

1. Yes
2. No

1❑ Dogs #:_____
2❑ Cats #: _____
3❑ Other #:_____

21. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).

1. steam or hot water
2. central gas furnace
3. wall or floor gas furnace
4. electric
5. other
6. don't know

OUTPATIENT RESPIRATORY PROPHYLAXIS

22. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?

1. Yes
2. No

23. Did this child receive a flu shot?

1. Yes
2. No

OUTPATIENT RESPIRATORY SUPPORT

24a. Is your child on any oxygen therapy (oxygen tank at home)?

1. Yes
2. No

IF **YES** TO QUESTION 24a:

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

*lpm = liters per minute

25. Is your child taking any medicines for asthma or wheezing?

1. Yes
2. No
3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as*: ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other _____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

THANK YOU FOR YOUR COOPERATION

SUPPORT FOLLOW ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED AT 18-22 MONTH FOLLOW UP VISIT

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing concerns your child may have.

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

4a. Has his/her chest ever sounded wheezy or whistling?
   1. Yes
   2. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?

1	2	3	4	5
Very rarely				On Most days

e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing _

g. Has this child's wheezing/whistling occurred as attacks?
   1. Yes
   2. No

h. Has this child ever been awakened at night by wheeze or by shortness of breath?
   1. Yes
   2. No

i. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

j. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

5. Does this child's chest sound wheezy or whistling during or shortly after vigorous exercise or crying?
   1. Yes, usually
   2. Yes, occasionally
   3. No

6a. Has he/she ever had episodes of shortness of breath or chest tightness?
   1. Yes
   2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6A:

b. Has this ever occurred when the child is at rest?
   1. Yes
   2. No

c. During the past year, how many episodes did he/she have?

1 2 3 4 5
Few Very many

d. How old was this child when he/she had the first such episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

OR: check here if the child still has condition: _

f. Has the child's chest ever sounded wheezy or whistling during episodes of shortness of breath or chest tightness?
   1. Yes
   2. No

g. Has he/she ever seen a doctor for shortness of breath or chest tightness?
   1. Yes
   2. No

h. Has this child ever taken any medicine for shortness of breath?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

7. Has this child ever had a cough when he/she did not have a cold?
   1. Yes
   2. No . . . SKIP TO QUESTION 6

IF **YES** TO QUESTION 5a

b. At what time of the day has this cough usually occurred? (CIRCLE ALL THAT APPLY) 1.
   1. In the morning, shortly after rising
   2. Later in the day
   3. During the night
   4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?
   1. Yes
   2. No

d. How often has this child been bothered by coughing?

1	2	3	4	5
Very Rarely				On most days

e. How old was the child when he/she first began to cough?
   ____ months

   OR: check here if child is still coughing: _

f. How old was this child when he/she stopped coughing?
   _____ months

g. Has the cough usually been dry or loose?
   1. Dry
   2. Loose

h. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?
   1. Yes
   2. No

i. How often has your child raised phlegm, sputum or mucus when coughing?
   1. Never
   2. Occasionally
   3. Often

j. Has he/she ever seen a doctor about the cough?
   1. Yes
   2. No

Does this child cough during or shortly after vigorous exercise?
   1. Yes, usually
   2. Yes, occasionally
   3. No

8a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 9a

IF **YES** TO QUESTION 8A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: _

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ _ months

OR: check here if doctor never said he/she had asthma: _

e. **During the past year**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past year**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

9a. Has your child ever had bronchitis?

1. Yes
2. No . . . SKIP TO QUESTION 10a

IF **YES** TO QUESTION 9a:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last episode occurred?

_____ months

OR: check here if child still has bronchitis ___

d. How old was this child when you were first told by a doctor that he/she had bronchitis?

_____ months

OR: check here if doctor never said he/she had bronchitis___

e. How often has this child had bronchitis?

1. one episode only
2. 2-3 episodes
3. 4 or more separate episodes
4. almost constantly

f. During the past year, how much trouble did he/she have with bronchitis?

1 2 3 4 5

None A great deal

g. During the past year, did this child take any medicine for bronchitis?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 254

10a. Has your child ever had croup?

1. Yes
2. No . . . SKIP TO QUESTION 11a

IF **YES** TO QUESTION 10a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of croup?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

11a. Has your child ever had bronchiolitis, or any wheezing illness in the first year of life not due to asthma?

1. Yes
2. No . . . SKIP TO QUESTION 12a

IF **YES** TO QUESTION 11A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

12a. Has your child **ever** had pneumonia?

1. Yes
2. No . . . SKIP TO QUESTION 13

IF **YES** TO QUESTION 12a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

13a. Was this child breast fed?

1. Yes
2. No . . . SKIP TO QUESTION 14

IF **YES** TO QUESTION 13a:

b. For how many months was this child breast fed?

1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

14a. Has the mother smoked at all since this child was born?

1. Yes
2. No . . . SKIP TO QUESTION 15a

IF **YES** TO QUESTION 14a:

b. For how many months did the mother smoke since this child was born?

_____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES)

_____ cigarettes
_____ pipes
_____cigars
_____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?

Never
Occasionally
Frequently

15a. Has the father smoked at all since the child was born?

1. Yes
2. No . . . SKIP TO QUESTION 16

IF **YES** TO QUESTION 15a:

b. For how many months did the father smoke since this child's birth?

_____ months

c. On the average, how many of each of the following did he smoke per day during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES).

_____ cigarettes
_____ pipes
_____ cigars
_____ non-tobacco cigarettes

d. How often has the father smoked in the same room with this child?

1. Never
2. Occasionally
3. Frequently

16. Did any other household member regularly smoke in the house since this child's birth?

1. Yes
2. No

17. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

18. How many brothers and sisters (including half siblings) does this child have?

_____

19a. Are there any other children living in your household **besides** this child and all of his/her siblings?

1. Yes
2. No . . . SKIP TO QUESTION 20

IF **YES** TO QUESTION 19a:

b. How many children other than this child and his/her siblings live in your house?

_____

20. Do you have any pets?
1. Yes
2. No

1❑ Dogs #:_____
2❑ Cats #: _____
3❑ Other #:_____

21. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).

1. steam or hot water
2. central gas furnace
3. wall or floor gas furnace
4. electric
5. other
6. don't know

OUTPATIENT RESPIRATORY PROPHYLAXIS

22. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?
1. Yes
2. No

23. Did this child receive a flu shot?
1. Yes
2. No

OUTPATIENT RESPIRATORY SUPPORT

24a. Was your child ever on any oxygen therapy (oxygen tank at home)?

1. Yes
2. No

IF **YES** TO QUESTION 24a:

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

*lpm = liters per minute

25. Is your child taking any medicines for asthma or wheezing?

1. Yes
2. No
3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as:* ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other _____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

ATOPY HISTORY

26. **During the past year**, for how many days has this child been unable to do his/her usual activities because of illnesses such as chest (not head) colds, bronchitis, asthma or pneumonia?

_____ days

27. How many head colds (common colds) **per year** does this child usually have?

1. Few (0-3 per year)
2. Some (4-5 per year)
3. Frequent (6-9 per year)
4. Constant (more than 9 per year)

28a. Has your child **ever** had hay fever or any other condition that makes his/her nose runny, stuffy, or itchy **apart** from colds?

1. Yes
2. No . . . SKIP TO QUESTION 29

IF **YES** TO QUESTION 28a:

b. How old was your child when you first noticed this condition?

_____ months

c. How old was this child when he/she stopped having this condition?

_____ months

OR: check here if child still has condition ~

d. When this child has the runny or stuffy nose, does he/she also usually:

Cough?	1. Yes 2. No
Wheeze?	1. Yes 2. No
Have shortness of breath?	1. Yes 2. No

29. Has this child **ever** had allergies which cause nose, eye or lung problems?

1. Yes
2. No

30. Has a doctor **ever** told you that this child had sinus trouble?

1. Yes
2. No

31a. Has this child **ever** been allergic to any food?

1. Yes
2. No

b. Has he/she **ever** been allergic to any medicine?

1. Yes
2. No

32a. Has this child **ever** had eczema (allergic skin rash)?

1. Yes

2. No . . . SKIP TO QUESTION 33a

IF **YES** TO QUESTION 32A:

b. Has a doctor told you this child had eczema?
1. Yes
2. No

c. At what age did the eczema begin?
_____ months

d. How old was this child when he/she last had eczema?
_____ months

OR: check here if child still has eczema ~

33a. Was this child breast fed?
1. Yes
2. No . . . SKIP TO QUESTION 34

IF **YES** TO QUESTION 33a:

b. For how many months was this child breast fed?
1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

34. At what age was formula introduced?
1. Never
2. less than 1 month
3. 1-3 months
4. 4-6 months
5. more than 6 months

35. At what age was cow's milk (nonformula) started?
1. Never
2. Less than 1 month
3. 1-3 months
4. 4-6 months
5. 7-9 months
6. 9-11 months
7. 12 or more months

36. At what age did he/she begin to receive table foods?
1. less than 1 month
2. 1-3 months
3. 4-6 months
4. 7-9 months
5. more than 9 months

THANK YOU FOR YOUR COOPERATION

From: Higgins, Rosemary (NIH/NICHD)
To: "alaptook@wihri.org"
Cc: "WOh@wihri.org"
Subject: Re: SUPPORT Secondary
Date: Monday, January 24, 2005 8:53:28 AM

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Abbot Laptook <ALaptook@WIHRI.org>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
CC: William Oh <WOh@WIHRI.org>
Sent: Mon Jan 24 08:51:55 2005
Subject: RE: SUPPORT Secondary

Rose
We should move forward with this secondary. Abbot

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 07, 2005 3:00 PM
To: Abbot Laptook; Abhik Das; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab
Cc: petrie@rti.org
Subject: SUPPORT Secondary

Hi,

Attached is a secondary study to SUPPORT For Pulmonary Follow Up. Please review this and send me a vote by January 24, 2005 for moving this forward to an ultimate financial/budget vote (You will be asked to vote on the budget items prior to next year's capitation awards).

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From:	Neil Finer
To:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"
Subject:	FW: RE: DSMC request
Date:	Friday, January 21, 2005 1:20:20 PM
Attachments:	DSMC jan 2005 .doc

Please use this data. Yesterday's was based on SErrors and we asked Abhik to redo. I think this gives more meaningful and useable proportions that we may want to recommend to the DSMC.
Many thanks
Be well
Neil

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, January 21, 2005 9:18 AM
To: Wade Rich; Neil Finer
Cc: Poole, W. Kenneth
Subject: FW: RE: DSMC request

Wade:

My conversation with you earlier today got me thinking, and I have also talked with Ken about this. Maybe you need to look at 2*SD, not 2*SE (standard error). (I used standard errors originally because that is what is used in computing confidence limits). So, the attached now has 2 columns added to the original table -- 2*SD and, what may be practically more useful, the range across the different network sites. Maybe these will better help you formulate the ranges.

Thanks

Abhik

Table 1: Proportion and 2 Standard Deviations for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	2 X SE	2X SD	Range of proportion across centers
IVH grade (3 or 4)	3753	0.237	0.014	0.850	0.108-0.371
DR Chest compressions	4050	0.108	0.010	0.621	0.035-0.258
Pneumothorax	3861	0.087	0.009	0.565	0.023-0.195
Death within first 14 days	4055	0.159	0.011	0.731	0.092-0.325

Table 2: Proportion and 2 Standard Deviations for infants with gestational age 24-25 weeks at birth

Variable	N	Proportion	2 X SE	2X SD	Range of proportion across centers
IVH grade (3 or 4)	1599	0.327	0.023	0.938	0.153-0.520
DR Chest compressions	1805	0.133	0.016	0.679	0.029-0.340
Pneumothorax	1667	0.116	0.016	0.640	0.026-0.239
Death within first 14 days	1808	0.249	0.020	0.865	0.124-0.485

Table 3: Proportion and 2 Standard Deviations for infants with gestational age 26-27 weeks at birth

Variable	N	Proportion	2 X SE	2X SD	Range of proportion across centers
IVH grade (3 or 4)	2154	0.170	0.016	0.751	0.022-0.263
DR Chest compressions	2245	0.088	0.012	0.567	0.034-0.200
Pneumothorax	2194	0.066	0.011	0.495	0.022-0.155
Death within first 14 days	2247	0.086	0.012	0.562	0.039-0.160

Note: The sample includes infants that were born on or after Jan 1, 2002 that have reached status.

From: Higgins, Rosemary (NIH/NICHD)
To: jobea0@chmcc.org
Subject: FW: RE: DSMC request
Date: Friday, January 21, 2005 1:01:00 PM
Attachments: DSMC jan 2005 .doc

Alan
Here are the rates of complications that RTI generated for help with SUPPORT

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, January 20, 2005 4:22 PM
To: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; Higgins, Rosemary (NIH/NICHD); 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'
Cc: nfiner@ucsd.edu
Subject: FW: RE: DSMC request

Hi All
I would like you to look at these. I would suggest that we use these estimates as limits below which we should not stop our trial. That is, if there is an increase in any arm of IVH, but the maximal occurrence is still within the 2 SD of Network experience that the trial, or that arm should not be stopped. This does not address the actual p value but rather the limits of the occurrence of these events.
I would appreciate your thoughts.
Be well
Neil

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, January 20, 2005 12:48 PM
To: Neil Finer; Rosemary Higgins
Cc: Poole, W. Kenneth
Subject: FW: RE: DSMC request

Neil and Rose:

Here is the information you wanted for the DSMC stuff. Note that the sample includes infants that were born on or after Jan 1, 2002 who have reached status, and the n's for each of these conditions are different because of differing numbers of missing values for each of them.

Let us know if you have any questions.

Thanks

Abhik

<<DSMC jan 2005 .doc>>

Table 1: Mean and 2 Standard Deviations for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	2 X Standard Deviation
IVH grade (3 or 4)	3753	0.237	0.014
DR Chest compressions	4050	0.108	0.010
Pneumothorax	3861	0.087	0.009
Death within first 14 days	4055	0.159	0.011

Table 2: Mean and 2 Standard Deviations for infants with gestational age 24-25 weeks at birth

Variable	N	Proportion	2 X Standard Deviation
IVH grade (3 or 4)	1599	0.327	0.023
DR Chest compressions	1805	0.133	0.016
Pneumothorax	1667	0.116	0.016
Death within first 14 days	1808	0.249	0.020

Table 3: Mean and 2 Standard Deviations for infants with gestational age 26-27 weeks at birth

Variable	N	Proportion	2 X Standard Deviation
IVH grade (3 or 4)	2154	0.170	0.016
DR Chest compressions	2245	0.088	0.012
Pneumothorax	2194	0.066	0.011
Death within first 14 days	2247	0.086	0.012

Note: The sample includes infants that were born on or after Jan 1, 2002 that have reached status.

From:	Neil Finer
To:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"
Cc:	nfiner@ucsd.edu
Subject:	FW: RE: DSMC request
Date:	Thursday, January 20, 2005 4:22:03 PM
Attachments:	DSMC jan 2005 .doc

Hi All
I would like you to look at these. I would suggest that we use these estimates as limits below which we should not stop our trial. That is, if there is an increase in any arm of IVH, but the maximal occurrence is still within the 2 SD of Network experience that the trial, or that arm should not be stopped. This does not address the actual p value but rather the limits of the occurrence of these events.
I would appreciate your thoughts.
Be well
Neil

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, January 20, 2005 12:48 PM
To: Neil Finer; Rosemary Higgins
Cc: Poole, W. Kenneth
Subject: FW: RE: DSMC request

Neil and Rose:

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Let us know if you have any questions.

Thanks

Abhik

<<DSMC jan 2005 .doc>>

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Death within first 14 days	2247	0.086	0.012

Note: The sample includes infants that were born on or after Jan 1, 2002 that have reached status.

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: DSMC Monitoring
Date: Wednesday, January 19, 2005 3:08:13 PM

Absolutely. I would like to see the data that I requested from Ken so that we could develop reasonable estimates of occurrence of certain outcomes.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, January 19, 2005 6:54 AM
To: Neil Finer
Subject: RE: DSMC Monitoring

Neil
Should we set up a call to get a more detailed document constructed, then send it to the steering committee?
I spoke to some of the NIH folks, and the more detailed we can make the document, the more constructive this can be if there is a concern with the study!
Thanks
Rose

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Saturday, January 15, 2005 1:51 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: DSMC Monitoring

Thanks Rose
I think we need to give careful thought to reasons that may lead to consideration of the premature stopping of SUPPORT. I appreciate your considering this issue.
Be well
Neil
----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
To: <nfiner@ucsd.edu>
Sent: Friday, January 14, 2005 10:49 AM
Subject: RE: DSMC Monitoring

> Neil
> The DSMC would make a recommendation to Dr. Alexander who would ultimately
> make the decision - I can run this by him to get some thoughts -
> Rose
>
> -----Original Message-----
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Friday, January 14, 2005 1:47 PM
> To: Higgins, Rosemary (NIH/NICHD)
> Subject: RE: DSMC Monitoring
>
> Hi Rose

> There is currently significant debate about whether a p value for stopping
> should be as stringent as the p value for efficacy. Using a lower p value
> for safety may lead to premature termination of a trial. I realize that
the
> traditional approach is to use a higher p value for safety, but this is a
> central issue in the debate of stopping a trial early.
> The Medical Research Council CRASH (Corticosteroids after significant head
> injury) RCT was designed to compare intravenous corticosteroids versus
> placebo in 20,000 adults with head injury. The DSMC for that trial
informed
> the Steering Group that steroids were associated with a 3.2% increase in
> mortality, from 17.9 - 21.1% (p = 0.0001), and this study was stopped
after
> 50% enrollment. Thus they used a much lower p value for stopping than the
> traditional p < 0.05 (Muzha, I.; Filipi, N.; Lede, R.; Copertari, P.;
> Traverso, C.; Copertari, A.; Vergara, E. A.; Montenegro, C.; deHuidobro,
R.
> R.; Saladino, P.; Surt, K.; Cizlzeta, J.; Lazzeri, S.; Lucero, L.; Pinero,
> G.; Ciccioli, F.; Videtta, W.; Barboza, M. F.; Svampa, S.; Sciuto, V.;
> Domeniconi, G.; Bustamante, M.; Waschbusch, M.; Gullo, M. P.; Posadas, A.;
> Linares, J. C. A.; Camputaro, L.; Penna, J.; Troccoli, G.; Galimberti, H.;
> Tallott, M.; Horn, S.; Eybner, C.; Buchinger, W.; Fitzal, S.; Oleffe, V.;
> Grollinger, T.; Delvaux, P.; Carlier, L.; Braet, V.; Jacques, J. M.;
> deKnoop, D.; Choi, H. K.; Schmitt, M.; Gentil, A.; Nacul, F.; Barrios, P.
> B.; Chen, X. K.; Hua, L. S., and et al. (Muzha I/Univ London London Sch
Hyg
> & Trop Med/CRASH Trials Coordinating Ctr/Keppel St/London WC1E
7HT/ENGLAND).
> Effect of intravenous corticosteroids on death within 14 days in 10008
> adults with clinically significant head injury (MRC CRASH trial):
randomised
> placebo-controlled trial. Lancet. 2004; 364(9442):1321-1328
>
> In ISIS-1, there was early evidence of increased mortality at a p < 0.05
> (Yusuf 2000) The DMEC did not to recommend stopping this trial which
> ultimately showed after the next 15,000 patients, that there was a 15%
> reduction in relative risk of mortality associated with beta blockade
after
> myocardial infarction (p < 0.01).
> I realize that we are not going to be convincing on changing such rules
but
> rather wanted you to know that there is not universal agreement that
> stopping for safety requires a higher p value than stopping for efficacy.
> Regards
> Neil
>
>
>
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> Sent: Friday, January 14, 2005 4:15 AM
> To: 'nfiner@ucsd.edu'
> Subject: Re: DSMC Monitoring
>
> Neil this is fine except p values for safety concern are set at 0.05,
> efficacy can be more stringent. I ca certainly get input from Jon and

jack.
> Thanks
> Rose
> ----------
> Sent from my BlackBerry Wireless Handheld
>
>
> -----Original Message-----
> From: Neil Finer <nfiner@ucsd.edu>
> To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>;
jobea0@chmcc.org
> <jobea0@chmcc.org>; aaf2@po.cwru.edu <aaf2@po.cwru.edu>;
> edward.donovan@cchmc.org <edward.donovan@cchmc.org>; mcw3@po.cwru.edu
> <mcw3@po.cwru.edu>; sduara@miami.edu <sduara@miami.edu>;
wcarlo@peds.uab.edu
> <wcarlo@peds.uab.edu>
> CC: petrie@rti.org <petrie@rti.org>; adas@rti.org <adas@rti.org>;
> poo@rti.org <poo@rti.org>; bkh@rti.org <bkh@rti.org>
> Sent: Fri Jan 14 01:54:39 2005
> Subject: Re: DSMC Monitoring
>
> Rose
> I would like to refine the estimates in this document. I have asked RTI to
> provide additional data from which we may be able to provide a better
> estimate of the limits. In addition perhaps we should provide an
indication
> of the p value utilized for such stopping if the values exceed these
limits.
>
> I would like this number to be very low $p < 0.001$. Another method is to
try
> to get the point estimates from the Cochrane for such events, but these
> would not be available for our specific study group and strata.
> Can we wait till we get these values before circulating? I would like John
> Tyson to review perhaps with Jack Sinclair.
> Your thoughts?
> Be well
> Neil
> ----- Original Message -----
> From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
> To: <jobea0@chmcc.org>; <aaf2@po.cwru.edu>; <edward.donovan@cchmc.org>;
> <mcw3@po.cwru.edu>; <nfiner@ucsd.edu>; <sduara@miami.edu>;
> <wcarlo@peds.uab.edu>
> Cc: <petrie@rti.org>; <adas@rti.org>; <poo@rti.org>; <bkh@rti.org>
> Sent: Thursday, January 13, 2005 8:30 AM
> Subject: DSMC Monitoring
>
>
> >
> > Hi,
> > I have attached the monitoring document for the DSMC - would you like it
> > shared with the steering committee?
> > Thanks
> > Rose
> > <<DSMC Monitoring.doc>>
> >
>

From: Higgins, Rosemary (NIH/NICHD)
To: poo@rti.org; adas@rti.org
Subject: FW: DSMC Monitoring
Date: Wednesday, January 19, 2005 2:25:00 PM

Ken and Abhik

Can we get this info? I would like to set up a call with the SUPPORT subcommittee so we can discussed a more detailed plan for recommended stopping rules.

Thanks

Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, January 13, 2005 4:07 PM
To: Higgins, Rosemary (NIH/NICHD); 'Edward Donovan'; 'ALAN JOBE'; sduara@miami.edu; WCarlo@peds.uab.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu
Cc: adas@rti.org; bkh@rti.org; petrie@rti.org; poo@rti.org; wrich@ucsd.edu; 'Maynard Rasmussen, MD'
Subject: RE: DSMC Monitoring

Hi All

By this email I am asking Ken and Abhik to provide use with the following information that we could use to develop guidelines for stopping rules.

Ken and Abhik - Can you provide use with the following based on the past 2-3 years of Network experience;

1 – the mean + 2 S Deviations for the occurrence of severe IVH (Gr 3 and 4)

2 – the mean + 2 SDev for the occurrence of DR compressions

3 – the mean + 2 SDev for the occurrence of pneumothoraces/air leaks in the first 2 weeks

4 – mean + 2 S Dev for death within the first 14 days

We would like to see all of these for the infants of 24 o/7ths weeks to 27 6/7ths weeks, and for each strata ie 24 0/7 to 25 6/7ths and 26 0/7ths to 27 6/7ths

Many thanks

Neil Finer

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, January 13, 2005 11:37 AM
To: Edward Donovan; ALAN JOBE; sduara@miami.edu; WCarlo@peds.uab.edu; aaf2@po.cwru.edu;

mcw3@po.cwru.edu; nfiner@ucsd.edu
Cc: adas@rti.org; bkh@rti.org; petrie@rti.org; poo@rti.org
Subject: RE: DSMC Monitoring

Thanks for the input so far – how about we modify the document at the subcommittee level and then get the steering committee to look at it??
Thanks

Rose

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Thursday, January 13, 2005 1:36 PM
To: ALAN JOBE; Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; WCarlo@peds.uab.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
Cc: adas@rti.org; bkh@rti.org; petrie@rti.org; poo@rti.org
Subject: RE: DSMC Monitoring

I agree with Wally's suggestions. In addition, I think that epi and/or chest compressions should be listed as "receipt of" rather than "need for". We have no way of measuring "need for".
We many want to adjust the proposed differerences in adverse event rates based on the expected underlying incidence and type of event. A 5% absolute difference in IVH likely calculates to a different RR compared to a 5% difference in death.

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

>>> "Wally Carlo, M.D." <WCarlo@peds.uab.edu> 01/13/2005 12:43:17 PM >>>
I have made some suggestions. What do you all think? We will need RTI help with the specifics. wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, January 13, 2005 10:31 AM
To: Alan Jobe (jobea0@chmcc.org); Av Fanaroff (aaf2@po.cwru.edu); Ed Donovan (edward.donovan@cchmc.org); Michele Walsh (mcw3@po.cwru.edu); Neil Finer (nfiner@ucsd.edu); Shahnaz Duara (sduara@miami.edu); Wally Carlo, M.D.
Cc: petrie@rti.org; adas@rti.org; Ken Poole (poo@rti.org); bkh@rti.org
Subject: DSMC Monitoring

Hi,
I have attached the monitoring document for the DSMC - would you like it shared with the steering committee?
Thanks
Rose
<<DSMC Monitoring.doc>>

Incoming mail is certified Virus Free.
Checked by AVG anti-virus system (http://www.grisoft.com).
Version: 6.0.825 / Virus Database: 563 - Release Date: 12/30/2004

Outgoing mail is certified Virus Free.
Checked by AVG anti-virus system (http://www.grisoft.com).
Version: 6.0.825 / Virus Database: 563 - Release Date: 12/30/2004

From: Higgins, Rosemary (NIH/NICHD)
To: Spong, Catherine (NIH/NICHD)
Subject: Re: FW: SUPPORT Protocol
Date: Wednesday, January 19, 2005 7:00:20 AM

We have several irb approvals, nhlbi funding, etc. Will they make a recommendation at their meeting next week? Thanks for following up!
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Spong, Catherine (NIH/NICHD) <spongc@dir49.nichd.nih.gov>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Tue Jan 18 20:54:27 2005
Subject: FW: FW: SUPPORT Protocol

FYI

Catherine Y Spong, MD
Chief, Pregnancy and Perinatology Branch
NICHD, NIH
6100 Executive Blvd, Rm 4B03, MSC 7510
Bethesda MD 20892 (Express mail: Rockville MD 20852)
Phone 301 435 6894
Fax 301-496-3790
Email: spongc@mail.nih.gov

-----Original Message-----
From: Jay Iams [mailto:iams-1@medctr.osu.edu]
Sent: Tuesday, January 18, 2005 6:29 PM
To: Spong, Catherine (NIH/NICHD)
Subject: Re: FW: SUPPORT Protocol

not yet - circulating to Concurrnt comm.
Jay

>>> "Spong, Catherine (NIH/NICHD)" <spongc@dir49.nichd.nih.gov> 1/13/2005 12:08:02 PM >>>

Jay - this was raised as an issue at the last SCM -- do we have any feedback for the NRN?
oxox
cathy

Catherine Y Spong, MD
Chief, Pregnancy and Perinatology Branch
NICHD, NIH
6100 Executive Blvd, Rm 4B03, MSC 7510
Bethesda MD 20892 (Express mail: Rockville MD 20852)
Phone 301 435 6894
Fax 301-496-3790
Email: spongc@mail.nih.gov

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD)
Sent: Thursday, January 13, 2005 9:59 AM
To: Spong, Catherine (NIH/NICHD)
Subject: FW: SUPPORT Protocol

Cathy

Here is the prior email about the SUPPORT Trial overlap - do you know if the MFMU concurrent research committee had a chance to weigh in?
Thanks

Rose

From: Higgins, Rosemary (NIH/NICHD)
Sent: Thursday, October 21, 2004 1:22 PM
To: Spong, Catherine (NIH/NICHD)
Subject: SUPPORT Protocol

Cathy

here is the protocol

I will let our PI's know that it is going to the MFMU concurrent research committee. It is randomized and if there is felt to be overlap, our concurrent research subcommittee (Jon Tyson, chair) may want to also weigh in. I believe the DR CPAP pilot was presented on several occasions at the MFMU meeting. I know I presented it once and did say we were developing a larger trial

Thanks

Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(for Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Secondary
Date: Monday, January 10, 2005 11:10:30 AM

I am in favor. wally

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 07, 2005 2:00 PM
To: Abbot Laptook (E-mail); Abhik Das; Wally Carlo, M.D.; Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab
Cc: petrie@rti.org
Subject: SUPPORT Secondary

Hi,
Attached is a secondary study to SUPPORT For Pulmonary Follow Up. Please review this and send me a vote by January 24, 2005 for moving this forward to an ultimate financial/budget vote (You will be asked to vote on the budget items prior to next year's capitation awards).
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD)
To: Phelps, Dale
Subject: RE: SUPPORT Secondary
Date: Friday, January 07, 2005 3:46:00 PM

Thanks

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Friday, January 07, 2005 3:45 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT Secondary

Thank you,

Our center has considered this protocol and vote to support it.

Dale Phelps
Rochester Center

> -----Original Message-----
> **From:** Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> **Sent:** Friday, January 07, 2005 3:00 PM
> **To:** Abbot Laptook (E-mail); Abhik Das; Carlo Waldemar (E-mail); Charles Rosenfeld; Phelps, Dale; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab
> **Cc:** petrie@rti.org
> **Subject:** SUPPORT Secondary
>
> Hi,
> Attached is a secondary study to SUPPORT For Pulmonary Follow Up. Please review this and send me a vote by January 24, 2005 for moving this forward to an ultimate financial/budget vote (You will be asked to vote on the budget items prior to next year's capitation awards).
> Thanks
> Rose
>
> Rosemary D. Higgins, M.D.
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine
> NICHD, NIH
> 6100 Executive Blvd., Room 4B03B
> MSC 7510
> Bethesda, MD 20892
> (For overnight delivery, use Rockville, MD 20852)
> 301-435-7909
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov

From:	Edward Donovan
To:	william_oh@brown.edu; ALAN JOBE; jlemons@iupui.edu; Higgins, Rosemary (NIH/NICHD) [E]; goldb008@mc.duke.edu; crosen@mednet.swmed.edu; sduara@miami.edu; barbara_stoll@oz.ped.emory.edu; wcarlo@peds.uab.edu; mcw3@po.cwru.edu; adas@rti.org; poo@rti.org; dstevenson@stanford.edu; nfiner@ucsd.edu; dale_phelps@urmc.rochester.edu; Jon.E.Tyson@uth.tmc.edu; Walid.Salhab@UTsouthwestern.edu; s_shankaran@wayne.edu; moshea@wfubmc.edu; alaptook@WIHRI.org; richard.ehrenkranz@yale.edu
Cc:	petrie@rti.org
Subject:	Re: SUPPORT Secondary
Date:	Monday, January 10, 2005 2:20:55 PM

I would like to see this secondary study move forward. I think the protocol still needs some work and would benefit from formal external review. I wonder to what extent the methods have been validated? I also wonder if we should consider more rigorous testing of pulmonary function at 18-22 months or perhaps later?

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 01/07/2005 2:59:43 PM >>>
Hi,
Attached is a secondary study to SUPPORT For Pulmonary Follow Up. Please review this and send me a vote by January 24, 2005 for moving this forward to an ultimate financial/budget vote (You will be asked to vote on the budget items prior to next year's capitation awards).
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: CHMCC Groupwise
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support - pulmonary outcomes
Date: Monday, January 10, 2005 8:10:36 AM

This secondary is important and seems well designed - but would be better with a limited amount of pulmonary function studies - perhaps in one or 2 centers - Ideally pulm f/u would be done at older ages, but...

Alan H. Jobe, MD, PhD
Professor of Pediatrics
Division of Pulmonary Biology/Neonatology
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From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; Abbot Laptook (E-mail); Abhik Das; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O"Shea; Michelle Walsh; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab
Cc: petrie@rti.org
Subject: Re: SUPPORT Secondary
Date: Saturday, January 08, 2005 1:35:25 PM

I vote in favor of this study. I believe that it will provide important additional information about pulmonary sequelae which will compliment the main trial.
Neil Finer

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Abbot Laptook (E-mail) ; Abhik Das ; Carlo Waldemar (E-mail) ; Charles Rosenfeld ; Dale Phelps ; Ed Donovan ; Ehrenkranz Richard (E-mail) ; Jobe Alan (E-mail) ; Lemons Jim (E-mail) ; Michael O'Shea ; Michelle Walsh ; Neil Finer ; Oh William (E-mail) ; Poole Kenneth (E-mail) ; Ronald GOldberg ; Shahnaz Duara ; Shankaran Seetha (E-mail) ; Stevenson David (E-mail) ; Stoll Barbara (E-mail) ; Tyson Jon (E-mail) ; Walid Salhab
Cc: petrie@rti.org
Sent: Friday, January 07, 2005 11:59 AM
Subject: SUPPORT Secondary

Hi,
Attached is a secondary study to SUPPORT For Pulmonary Follow Up. Please review this and send me a vote by January 24, 2005 for moving this forward to an ultimate financial/budget vote (You will be asked to vote on the budget items prior to next year's capitation awards).
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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301-435-7909
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From: Michael O`Shea
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Secondary
Date: Friday, January 07, 2005 3:14:59 PM

Rose,
I vote yes.
Mike.

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 07, 2005 3:00 PM
To: Abbot Laptook (E-mail); Abhik Das; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O`Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab
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Cc:	petrie@rti.org
Subject:	SUPPORT Secondary
Date:	Friday, January 07, 2005 2:59:00 PM
Attachments:	SUPPORT Follow-on Study 10-1 (2).doc Costs for Follow-on.xls Budget Justification.doc Appendix A.doc Appendix B.doc Appendix C.doc

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NICHD SUPPORT Trial Follow-on Study of Outpatient Pulmonary Outcomes

University of Rochester
Golisano Children's Hospital at Strong

Timothy P. Stevens, MD
Peter Szilagyi, MD, MPH
Dale Phelps, MD

Proposal Updated: October 1, 2004

Contact Information:

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A. ABSTRACT

Statement of Problem Premature infants have a greater risk for wheezing and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor for later wheezing, the etiology of recurrent wheezing in formerly premature infants is not known.

Hypotheses The goal of the clinical project detailed here is to understand better the antecedents of recurrent wheezing among preterm infants during early childhood by evaluating the effect of treatment with different levels of targeted oxygen saturation in the immediate neonatal period. **The overarching hypothesis is that premature infants exposed to supplemental oxygen suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater symptomatic airway dysfunction when challenged with subsequent environmental or infectious exposures.**

Hypothesis #1- Relative to infants managed with a higher SpO2 range, infants who are managed with a lower targeted SpO2 range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' corrected age (CA) whether they develop CLD or not.

Hypothesis #2- Relative to infants managed with prophylactic surfactant and conventional ventilation, infants who are managed with the early use of CPAP and a permissive ventilator strategy will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' CA whether they develop CLD or not.

Design

Longitudinal follow-up of infants enrolled in the SUPPORT Trial to determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the prevalence of recurrent wheezing and volume of outpatient pulmonary care in the first 18 months' CA.

Definition of outcomes:

A) Parental Report of Wheezing
B) Physician Diagnosed Wheezing.
C) Volume of Outpatient Pulmonary Care including number of pulmonary medications, office and emergency room visits and re-hospitalizations for respiratory illnesses.

Ascertainment of outcomes:

Outcomes will be measured at 4 time points in the first 18-22 months' CA as follows:

1. NICU discharge -baseline interview at to obtain family and environmental history
2. Six months' CA - telephone interview to ascertain prevalence of wheezing and obtain interval history of need for pulmonary care.
3. Twelve months' CA - telephone interview as at 6 months'
4. 18-22 months' CA- Prior to NICHD follow-up clinic visit, a telephone interview to ascertain prevalence of wheezing and obtain interval history of need for pulmonary care will be administered and primary care physician contact information collected for outpatient office chart review.
5. Outpatient chart review- data extraction from patient outpatient medical record.

Anticipated Results

We anticipate that, for infants who develop CLD and those who do not, treatment with a lower vs. higher targeted oxygen saturation range will result in less frequent episodes of wheezing and less need for outpatient pulmonary care in the first 18-22 months' CA.

Benefits and Risks

The proposed SUPPORT Follow-on Pulmonary Outcome Study will directly measure symptomatic airway dysfunction and outpatient pulmonary morbidity in infants treated with either a higher vs. lower targeted oxygen saturation. These data will provide important insight into the effect of different levels of supplemental oxygen exposure on airway growth and development in formerly premature infants. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the neurodevelopmental follow up visit. We anticipate no risk to the patient of this observational follow-on study.

B. STATEMENT OF THE PROBLEM

Premature infants have a greater risk for wheezing and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor for later symptomatic airway dysfunction, the etiology of recurrent wheezing in formerly premature infants is not known.

C. HYPOTHESES

The overarching hypothesis is that premature infants exposed to supplemental oxygen and, to a lesser extent, mechanical ventilation, in the neonatal period suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction and respiratory symptoms when challenged with subsequent environmental or infectious exposures.

Specific Hypotheses:

Hypothesis #1- We hypothesize that relative to infants managed with a higher SpO2 range, infants managed with a lower SpO2 range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care at 18-22 months' CA.

Hypothesis #2- We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

Hypothesis #3- We hypothesize that **among infants with CLD**, infants managed with a lower SpO2 range relative to those managed with a higher SpO2 target range will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

Hypothesis #4- We hypothesize that **among infants without CLD**, infants managed with early use of CPAP and permissive ventilator strategy relative to infants managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic wheezing and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

D. SPECIFIC AIMS

The goal of this project is to understand better the etiology of recurrent wheezing among formerly premature infants during early childhood by examining the interaction of oxygen exposure (targeted SpO2 range), surfactant therapy and early nasal CPAP in the newborn period.

SA#1 - Measure the effect of lower vs. higher targeted SpO2 on the prevalence of recurrent wheezing and volume of outpatient pulmonary care among infants born $24^{0/7}$ - $27^{6/7}$ weeks' gestation during the first 18-22 months' CA.

SA#2 - Measure the effect of early CPAP and permissive ventilator strategy compared with prophylactic surfactant and traditional ventilator strategy on the prevalence of recurrent wheezing and volume of outpatient pulmonary care among infants born 24-27 weeks' gestation during the first 18-22 months' CA.

SA#3 – Among infants who develop CLD, determine whether CLD is milder in infants managed with low compared with high targeted SpO2 by measuring recurrent wheezing and volume of outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

SA#4 – Among infants who do not develop CLD, determine whether pulmonary outcome is better for infants managed with a low compared with high targeted SpO2 range by measuring the prevalence of recurrent wheezing and need for outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory

strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

E. RATIONALE/JUSTIFICATION

Although synergy in producing airway injury may exist between oxygen toxicity and mechanical forces applied to the lung, animal and human data suggest that exposure to high concentrations of supplemental oxygen alone is sufficient to cause airway narrowing and greater reactivity to subsequent challenges. Understanding the relative contributions of oxygen toxicity and mechanical forces on airway growth and development may facilitate development of targeted therapies for preventing or reducing symptomatic airway dysfunction in premature infants.

Why measure recurrent wheezing and outpatient pulmonary care as an outcome from a clinical NICU interventional trial?

1) Important information will be available on the effect of oxidant gas exposure on airway development and later symptomatic airway dysfunction. Exposure to oxidant gas has been causally linked with later wheezing. Existing data on the relationship between supplemental oxygen therapy and wheezing come from longitudinal cohort studies, a design that suffers from intrinsic limitations that make controlling for potential confounders of respiratory outcome difficult. By randomizing infants to higher vs. lower target saturation ranges, and thereby presumably higher or lower concentrations of inspired oxygen, *the SUPPORT Trial creates a unique, and perhaps the only, opportunity to evaluate the effect of different levels of supplemental oxygen on subsequent symptomatic airway dysfunction and need for outpatient pulmonary care after NICU discharge.*

2) Using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care can be directly quantified, allowing assessment of whether infants both with and without CLD have improved pulmonary health as a result of the study intervention.

3) The incidence of CLD, defined as an oxygen requirement at 36 weeks' PMA, is an incomplete measure of pulmonary outcome in formerly premature infants during early infancy. CLD as defined above reflects alveolar gas diffusion and NICU oxygen needs. However, outpatient pulmonary morbidity for formerly premature infants is often airway related, involving wheezing either as a primary symptom such as bronchiolitis or as a complicating symptom of lower respiratory tract infection such as pneumonia. The studies proposed here will directly measure the effect of a randomized NICU-based clinical intervention on symptomatic airway dysfunction and outpatient pulmonary morbidity.

4) The risk of a negative trial is reduced. Because the diagnosis of CLD does not completely predict need for outpatient pulmonary care, clinically significant improvements in pulmonary morbidity may occur with minimal or no change in the incidence of CLD. This result has occurred in other interventional trials in which no difference in CLD were observed (12).

5) At present, there is no standard way to measure symptomatic airway dysfunction in premature infants in NICHD pulmonary intervention trials. There is need for a better measure to assess clinical pulmonary outcome to recognize and promote therapies that reduce need for outpatient care of former extremely premature infants.

6) By measuring outpatient pulmonary outcomes, the cost-effectiveness of the SUPPORT study interventions can be assessed. It is reasonable to expect that the SUPPORT Trial interventions will improve outpatient pulmonary outcomes for infants who ultimately develop CLD as well as those who do not. This proposed follow-on study collects the primary data necessary to quantify the cost-effectiveness of this therapy.

F. BACKGROUND / PREVIOUS STUDIES

Recurrent Wheezing In Preterm Infants is a Significant Public Health Problem

Outpatient pulmonary morbidity, especially recurrent wheezing and need for outpatient pulmonary care, is an understudied but clinically important outcome measure for former premature infants with and without CLD. Infants born weighing < 1500 grams (very low birth weight, VLBW) and especially infants born weighing < 1000 grams are at increased risk for small airway narrowing, airway hyperreactivity, wheezing, and nighttime cough (1-11). Up to 30-40% of formerly extremely premature infants have episodes of wheezing after NICU discharge with many requiring bronchodilators and frequent health care visits. Up to 40-50% of premature infants require re-hospitalization, mostly for treatment of respiratory illnesses (9;12;13). In analysis of cross sectional data from the National Maternal Infant Health Survey and 1991 Longitudinal Follow up Survey, the prevalence of asthma-like recurrent wheezing varied markedly with birth weight. Infants with normal birth weight (NBW, > 2500 grams) had a 6.7% prevalence of asthma compared to 10.9% of low birth weight infants (LBW, 1500-2499 grams) and 21.9% for VLBW (14). Mean per capital asthma related costs have been estimated to be 5 times greater for VLBW compared with NBW infants. The net effect is that VLBW infants, who comprise 2% of asthma patients, consume up to 7% of asthma-related therapy costs (14).

Animal Studies

Animal studies suggest that exposure of the premature lung to hyperoxia (without concomitant mechanical ventilation) for relatively brief periods is sufficient to cause airway remodeling and smooth muscle changes that predispose toward airway narrowing and hyperreactivity to subsequent environmental challenges (15-18). In a rhesus monkey model of asthma, Schlegle et al. exposed infant monkeys to repeated cycles of inhaled House Dust Mite Allergen (HDMA), ozone or filtered air. While repeated exposure to either ozone or HDMA had mild effects, exposure to cycles of ozone followed by HDMA resulted in asthma like changes with significant increases in serum IgE, serum histamine, peripheral eosinophilia and greater airway reactivity. Using supplemental oxygen rather than the stronger oxidant ozone, Schulman et al. found that exposure of newborn guinea pigs to 70% oxygen for 96 hours resulted in airway hyperreactivity at 2 and 9 days after the cessation of oxygen. In cell models, intracellular glutathione buffers airway cells against oxidant injury during hyperoxia (19;20). Although the critical period for lung development is comparatively brief in laboratory animals compared with human infants, the duration of hyperoxic exposure (and risk of oxygen toxicity) for treatment of neonatal lung disease may extend for much longer periods in premature infants known to be deficient in anti-oxidant systems such as intracellular glutathione.

Premature Infants <u>With CLD</u> Are At Greatest Risk For Recurrent Wheezing

Among premature infants, infants with bronchopulmonary dysplasia (BPD) are at highest risk for poor pulmonary outcome after NICU discharge. Infants with CLD have small airway compromise with decreased forced expiratory flow velocities, airway hyperreactivity, and increased functional residual volume suggesting airway obstruction (2;5;9;21-24). In a pulmonary follow up of infants with HMD or BPD, De Klein et al. found infants with BPD had reduced FEV1 at baseline while infants with RDS but not BPD had significant improvements in FEV1 following bronchodilator therapy. In this study, a history of recurrent wheezing predicted abnormal pulmonary function (25). In a recent study of infants with CLD, Robin et al. found that 50% of infants with CLD had symptoms of recurrent wheezing and 35% showed significant airway responsiveness to bronchodilators, evidenced by a 24% increase in forced expiratory flow velocity at 75% of expired forced vital capacity (FEF_{75}). This study demonstrated the relationship between recurrent wheezing as a clinical symptom and the physiologic measurement of airway obstruction. Infants with CLD and a history of recurrent wheezing showed greater expiratory flow limitation, hyperinflation, and airway responsiveness to albuterol compared to those without a history of recurrent wheezing (24).

Premature Infants Without CLD Have Significant Airway Dysfunction

Among VLBW infants who do not develop CLD, several studies of pulmonary outcome have found an association between neonatal oxygen exposure and increased prevalence of expiratory flow dysfunction and airway hyperreactivity (4;11;26-29). Some authors attribute reductions in airway function to intrinsically small airways as a consequence of poor intrauterine growth rather than superimposed airway injury or reactivity from neonatal respiratory disease (1;30). However, because small airways alone do not fully explain findings of airway hyperreactivity, other mechanisms of small airway dysfunction are necessary to explain respiratory symptoms.

Several pulmonary outcome studies have reported significant increases (2-fold or more) in airway obstruction among VLBW infants without CLD following exposure to as little as an FIO2 of 0.4 for 5 days (3;4;8;26). Not all studies have had similar results suggesting variability in effect or susceptibility of babies to oxygen exposure (31;32). In 1982, Coates et al. described increased small airway resistance at 10 year follow up of mildly premature infants (mean gestational age 31 weeks and birth weight 2000 grams) treated with a high oxygen (O2) regimen and those exposed to a low O2 regimen for the treatment of respiratory distress syndrome (RDS). Mechanical ventilation was not used in either group. Pulmonary function tests were performed on survivors receiving either the low or high supplemental oxygen regimen ten years after their initial illness. Infants treated with high levels of supplemental oxygen alone (no mechanical ventilation) had decrements in airway function similar to decrements in function reported for a historical cohort of RDS survivors treated with ventilation and high levels of supplemental oxygen. From these data, the authors concluded that neonatal exposure to high oxygen concentrations in the absence of mechanical ventilation is capable of causing long-term change in small airways (28). These studies suggest that use of lower supplemental oxygen concentration may improve respiratory health of infants who do not develop CLD.

Premature Infants Without CLD Have Increased Risk of Recurrent Wheezing and Need for Outpatient Pulmonary Care.

For VLBW infants without CLD, the prevalence of parental or physician reported wheezing is increased compared with term infants, with estimates of the prevalence of wheezing ranging from 10-38% (4;8). Prevalence of wheezing requiring medications is greater compared with term infants. VLBW infants have a 2-4-fold increase in respiratory related re-hospitalization rates compared with term infants (4;8;33-35). Although most studies have found the risk of recurrent wheezing remains elevated throughout childhood, an Australian longitudinal follow-up cohort of VLBW infants found the prevalence of wheezing remained elevated for 2 years then returned to baseline (32;36).

Prevalence of Symptomatic Airway Dysfunction in Formerly Preterm Infants During the Surfactant Era Remains High

With the advent of surfactant therapy, survival for small infants increased dramatically and the incidence of CLD changed minimally (37-40). Classic BPD evolved into the new CLD characterized by reduced alveolarization and more variable airway changes (41). Pulmonary follow up studies during the surfactant era showed reduced pulmonary morbidity in surfactant treated patients. Typical of these studies, Sell et al. found the incidence of asthma was significantly lower in infants given synthetic surfactant compared with those given air placebo. Pelkonen et al. performed PFT measurements on 40 children aged 7-12 years who were born before 30 weeks of gestation with an immature surfactant system, and were randomized to one of three treatment groups: prophylactic surfactant, rescue surfactant and placebo (air). Spirometric parameters of preterm born children were compared with those of 20 children born at term. Bronchial obstruction was found in 53% of the prophylactically treated group, in 36% of the rescue group, in 67% of the placebo group, and in 0% of the control group (42). A recent report suggests that the introduction of surfactant therapy markedly altered the pulmonary outcome of premature infants. Published in 2001, the Newborn Lung Function Project Group reported results of a prospective 12-year follow-up of VLBW infants following the introduction of surfactant therapy. Among infants with CLD, wheezing symptoms decreased from 50 to 16% from the period before compared with the period after surfactant therapy became available. However, among infants without CLD the prevalence of wheezing increased from 14% to 38% with the introduction of surfactant. These data suggest that surfactant therapy has an effect on outpatient respiratory health and underscores the need to

consider outpatient pulmonary outcomes in evaluating therapeutic strategies that potentially decrease surfactant replacement therapy.

CLD is an Incomplete Predictor of Outpatient Pulmonary Morbidity

Several authors have looked to respiratory symptoms and need for outpatient pulmonary care as outcome measures for neonatal lung disease (9;10;12;24). In 1988, from a retrospective chart review of 605 premature infants < 1500 grams, Shennan et al. found that the presence of BPD (oxygen requirement at 36 weeks PMA) had a 63% positive predictive value and a 90% negative predictive value for abnormal pulmonary outcome in the first 2 years of age. However, this study from before the era of exogenous surfactant therapy defined abnormal pulmonary outcome as death, oxygen requirement at 40 weeks PMA, 2 or more respiratory related hospital admissions, wheezing requiring drug therapy or persistent wheezing resulting in growth failure, handicap or hypotonia at 1 year of age. Such restrictive criteria for abnormal pulmonary outcome are likely to underestimate the burden of recurrent wheezing on former premature infants and their families. Several recent interventional studies show that CLD is an incomplete predictor of clinical wheezing and need for outpatient pulmonary care and suggest that differences in oxygen exposure or oxidant stress may affect pulmonary outcome without affecting the incidence of CLD.

Interventional Trials That Did Not Reduce CLD But Did Reduce Outpatient Pulmonary Morbidity.

Recent data in preterm infants treated with human recombinant superoxide dismutase (SOD) found that anti-oxidant therapy did not reduce the incidence of CLD. However, among infants < 27 weeks gestation SOD therapy resulted in significant reductions in the first year after NICU discharge in the number of emergency room visits and number of re-hospitalizations for respiratory problems and reductions in the need for bronchodilators suggesting a reduced prevalence of wheezing in patients treated with SOD (12). In a randomized, multi-center trial from Helsinki, N acetyl cysteine did not reduce the incidence of CLD. Outpatient pulmonary outcome of these patients has not been reported.

Treatment of Premature Infants With Higher Targeted Oxygen Saturations Is Associated with Poorer Pulmonary Outcome

In the STOP-ROP Study, infants exposed to higher levels of oxygen to achieve a targeted saturation of 96-99% compared with 89-94% had greater risk of adverse pulmonary events including pneumonia, chronic lung disease exacerbations and need for diuretics, oxygen and hospitalization at 3 months'' corrected age. *Although all infants in this study had CLD at enrollment, different targeted oxygen saturation were associated with large differences in pulmonary morbidity.* Adverse pulmonary outcomes occurred with differences in FIO2 of as little as 10% for patients treated with ventilation, CPAP or hood (36% $\pm$ 14% vs. 46% $\pm$ 20%, respectively for low vs. high saturation range) and 5% for infants treated with nasal cannula, (26% $\pm$ 6% vs. 31% $\pm$ 11%, respectively for low vs. high saturation range) (44). In a similar study, The Benefits of Oxygen Saturation Targeting (BOOST) Trial randomized infants < 30 weeks' gestation to higher (95-98%) or lower (91-94%) saturations ranges beginning at 32 weeks' PMA to determine whether infants managed with higher targeted saturation range showed better growth and neurodevelopment. As in the STOP-ROP study, need for oxygen therapy was prolonged. Trends towards an increased risk of pulmonary death and fewer outpatient office visits (median 27.5 vs. 31.3, $p < .11$) were seen in the lower targeted oxygen saturation group (13).

G. METHOD/ PROCEDURES

NICHD SUPPORT Trial Follow-on Study of Pulmonary Outcomes

G.1 Description of study design

This study will add an 18-22 month longitudinal, prospective follow-on study of surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial.

G.2 Definition of study population

Infants with gestational age of $24^{0/7}$-$27^{6/7}$ weeks' gestation by best obstetrical estimate.

Inclusion criteria:

- Full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Parents/legal guardians have provided consent for enrollment
- No known major congenital malformations
- Survival to hospital discharge

Exclusion Criteria

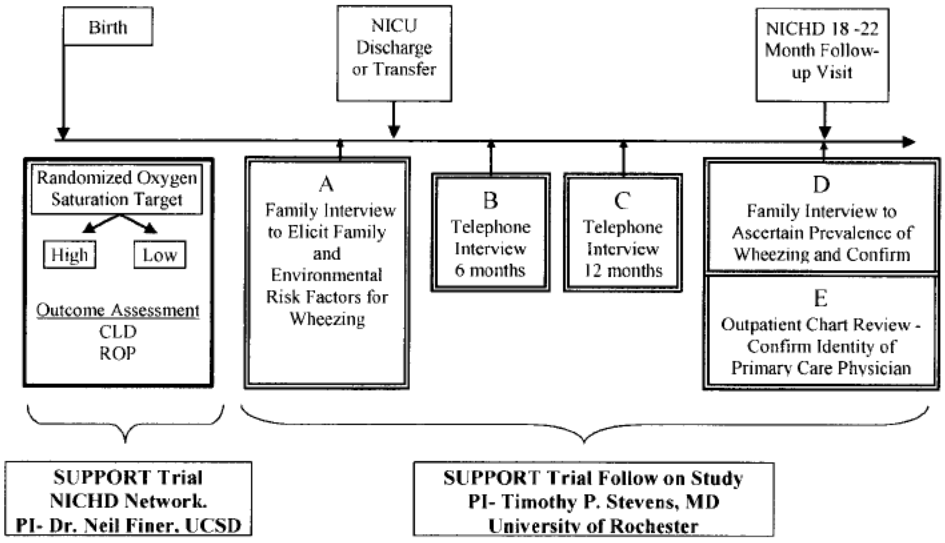
- Transport to the center after delivery
- Parents/legal guardians refuse consent
- Research apparatus/study personnel are not available.
- Gestational age $< 24^{0/7}$ or $\geq 28^{0/7}$ weeks' gestation

G.3 Description of study intervention

Before delivery, infants will be randomized to subsequent management with high vs. low target oxygen saturation according to the SUPPORT Protocol. The SUPPORT Follow-on Study proposed here begins just prior to NICU discharge (Figure 1).

SUPPORT Trial Follow-on Study

Figure 1. **Infants $24^{0/7}$-$27^{6/7}$ Weeks' Gestation**



"A" will be administered at NICHD Network Centers

"B-E" will be conducted long distance by University of Rochester research staff.

Fig 1, A. Parent (Guardian) Interview to Elicit Family and Environmental Risk Factors for Wheezing The family interview will be administered at each participating Network Center by site study nurses prior to NICU discharge or transfer. The questions are based on intake questions used by the Tucson Respiratory Study and are designed to elicit family history of asthma, atopy, and home environment and to identify likely care givers (Questionnaire in Appendix G). Consent for release of medical information will be obtained to facilitate contacting physician offices to obtain office data.

Fig 1, B. Telephone Interview at 6 months' CA – respiratory interval history

Fig 1, C. Telephone Interview at 12 months' CA – respiratory interval history

Telephone interviews will be undertaken at 6 and 12 months' to obtain limited interval history of respiratory problems including wheezing, medications used, and health services sought for respiratory related problems (Questionnaire in Appendix H).

Fig 1, D. Parental Interview to Ascertain Prevalence of Wheezing and Confirm Risk Factors This parent interview will also be administered by telephone, prior to the regularly scheduled 18-22 month NICHD developmental follow up clinic visit (an NICHD funded, ongoing program). Contacting parents prior to the office visit will help improve the Developmental Follow Up Clinic attendance rate and will allow the clinic visit to provide a back up means to contact the family. All telephone interviews, the 2 limited telephone interviews and the second family history interview at 18-22 months', will be conducted long distance from Rochester (see below). The interview questionnaires are based on questionnaires administered by the Tucson Respiratory Study at approximately one year of age (Questionnaire in Appendix I). Questions are designed to ascertain the frequency and severity of wheezing episodes. In addition, risk factors obtained at the 1st interview will be confirmed or updated.

Fig 1, E. Outpatient Chart Review - Confirm Identity of Primary Care Physician

To confirm results of physician report of wheezing obtained by telephone interview, patients undergoing telephone interview will have their primary care physician's medical record reviewed.

E.1 – Physician report of wheezing

E.2 – Frequency of outpatient pulmonary care. The volume of outpatient pulmonary care including outpatient primary care physician office visits, pulmonary specialty care, emergency room visits, hospitalizations and the number and duration of pulmonary medications will be obtained from primary care physician chart review. To help assure compliance by primary care office staff, a $25 honorarium will be offered for successful completion of the chart review form (45-47).

G.4 Precise definition of primary/secondary outcomes

1) Definition Of Parental Report Of Wheezing. The primary outcome will be parental report of recurrent wheezing, defined as more than 1 episode of wheezing, using questions adapted from the Tucson Children's Respiratory Study, questions validated in a large prospective birth cohort study of term infants (48-54) (Appendices G-I). The primary question used in the telephone interview for this project will be the same as the one used in the Tucson Children's Respiratory Study "Did your child have wheezing?" (48) Additional questions will be used to further characterize the wheezing episodes, identify wheezing associated with a viral illness (parental report of a "cold") and wheezing associated with environmental exposures. The prevalence of health services utilization (outpatient office visits for pulmonary care, ER visits, re-hospitalizations, bronchodilator therapy) for pulmonary reasons will also be collected during interviews. The Tucson study also ascertained frequency of office visits and use of respiratory medications. Of full term infants whose parents reported that their infant had an episode of wheezing, 40% had recurrent wheezing in the first 6 years compared with 22% of infants whose parents reported no episodes of wheezing in the first 3 years.

Parental Report of Wheezing Is A Reliable Outcome Measure of Airway Dysfunction

Evaluation of frequency and severity of respiratory symptoms and volume of pulmonary care has been used as the primary outcome in multiple follow up studies of term and premature infants (10;12;14;43). A recent review evaluated the value of respiratory symptom history ascertained by parental questionnaire in determining the risk for developing asthma in early childhood. By evaluating 9 large, longitudinal, full term birth cohort studies and reviewing the original questionnaire from 7 of these studies, Koopman found that the questions posed to parents

eliciting a history of wheezing in their infants were similar. Parental report of wheezing predicted an increased risk for later respiratory symptoms including asthma. In the studies proposed here, recurrent wheezing ascertained by parental report will be used as the primary outcome, rather than physiologic measurements of airway dysfunction, for several reasons (Table 3). Although the goal of using respiratory questionnaires in the studies proposed here is to measure pulmonary outcome, not to predict asthma, studies of asthma questionnaires and their ability to predict asthma demonstrates the validity of parental report of wheezing as an accurate measure of airway dysfunction.

Reasons to Use Parental Report of Wheezing as Primary Outcome Measure

- Parental interview can be performed more readily on large numbers of patients. The validity of this approach has been shown in several longitudinal studies including The Tucson Respiratory Study, upon which the interview questions are based.
- Recurrent wheezing is highly correlated with changes on pulmonary function testing. In a study of infants with CLD, a history of recurrent wheezing was associated with greater expiratory flow limitation, hyperinflation and airway responsiveness to albuterol on pulmonary function testing compared to those without a history of recurrent wheezing (24).
- Parental recall of respiratory illnesses has been shown to correlate strongly with review of medical office records. For asthma and bronchitis in the past year, Pless et al. found good agreement between recall of 288 parents and physician office chart review. Parental education and occupation were not predictive of a parent's ability to recall the illness (55). In an assessment of parental recall done to evaluate minor injury in children, Harel found recall declined with time, with the best recall occurring in the first 3 months' after injury with further decline after 6 months' from the time of the injury (47;56;57).

Advantages of Conducting Telephone Interviews From a Single Center

Conducting the telephone interviews from Rochester will:

1) require less effort from the individual Network Centers (Network Centers may assist in tracking families)
2) allow standardization of the telephone interview by a core group of trained interviewers
3) blind the telephone interviewer to the SUPPORT Trial study group designation
4) reduce the cost of the study by consolidating the telephone training and follow up at one site.

2) Definition Of Physician Diagnosed Wheezing. A secondary outcome will be physician report of recurrent wheezing, defined as more than 1 episode of wheezing. Physician diagnosed wheezing will be collected by parental report during telephone interviews using the question "Did a doctor tell you your child had wheezing?" and "Where did you see that Doctor, primary care, emergency room, hospital or other?" In addition, review of the primary care physician medical chart will be undertaken to identify episodes of physician documented wheezing.

3) Definitions of Secondary Outcomes - Measures of Volume of Outpatient Pulmonary Care

Important secondary outcomes of outpatient pulmonary morbidity will be collected (Table 1).

Table 1. ***Secondary Outcomes, Covariates and Sources***	
Outcomes	**Source**
Secondary Outcomes	
Number and duration of outpatient pulmonary medications including bronchodilator, diuretic, methylxanthine, and inhaled and systemic steroid therapy.	Family interview, primary care chart review
Number of office visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of emergency room visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Number of re-hospitalizations for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview, primary care chart review
Growth at 18 months' CA (height, weight and head circumference)	NICHD follow up clinic data

Data Collection: Ascertainment of Outcomes - Field Work

Ascertainment of Wheezing and Outpatient Pulmonary Morbidity By Telephone Interview.
There will be 4 parental interviews over 18-22 months', one prior to NICU discharge and 3 subsequent telephone interviews at 6 month intervals to collect data on the prevalence of recurrent wheezing, need for outpatient pulmonary care, and relevant environmental and family history covariates (Figure 1, A-D above). Based on review of longitudinal studies of full term infants in which follow up patient contacts occurred quarterly to once every 18 months', a 6 month interval for follow up patient contacts is planned in an effort to reduce parental recall omissions which are more likely to occur with less frequent follow up (43;56). The 4 interviews are designed to collect the primary and secondary outcomes of the follow-on study. Other inpatient and outpatient data will be collected as part of the NICHD Neonatal Research Network Generic Database (GDB) and Follow-up Program.

The University of Rochester Neonatology Research Group has conducted similar telephone interview designs as part of an ophthalmologic outcome study of patients enrolled in a randomized trial of cryotherapy to treat ROP and a 15-year, longitudinal neurological assessment conducted by telephone survey among 132 infants treated with surfactant. Telephone follow up rates were 96% follow up at 7 years and 95% follow up at 15 years (58). In the study proposed here, the University of Rochester Health Services Research Group (HSR Group), will conduct the telephone interviews.

In telephone follow up surveys conducted by the HSR Group, follow up rates at 12 months' have exceed 75% in populations at high risk for being lost to follow up (59-65). The Rochester HSR Group has over 2,500 square feet of newly renovated space. Under the direction of Drs. Jonathan Klein and Peter Szilagyi, the HSR group includes sufficient space and all appropriate equipment and personnel to perform telephone interviews and database management for the project presented here. The HSR Group will conduct 3 telephone interviews from Rochester. Drs. Peter Szilagyi and Jonathan Klein, co-directors of the HSR Group, are mentors for Dr. Stevens' K23 Patient Oriented Research Award application. Drs. Klein and Szilagyi will work with Dr. Stevens and Dr. Phelps in the implementation and management of the tracking and respiratory questionnaire program. To facilitate tracking and record keeping, Dr. Stevens will design and write a database to track enrolled patients and their contact information, next scheduled interview, and record answers to phone interview questions. Each interview will close with a question as to whether the family plans a new address or phone number prior to the next interview. The names and phone number of a friend or relative and their primary care physician will be sought so that they may be contacted in the event that contact with the patient is lost. By interviewing families every 6 months', a higher follow up rate will be achieved because family contact information will not become so out of date that the family is lost or that re-contacting them is inefficient. We anticipate that each interview will require 2 hours of staff time, with 20-30 minutes to conduct the interview and 90 minutes to contact family and enter data.

Interview Instruments – (Appendices A-C) Questionnaires based on the Tucson Children's Respiratory Study, a well validated questionnaire used in a large longitudinal cohort study that followed healthy full term infants from birth to over 20 years of age. The questionnaires have been updated to reflect currently available respiratory medications and modified to address the health issues that are faced by formerly premature infants such as use of palivizumab for RSV prophylaxis. In addition, the questionnaires are designed to elicit a thorough history of possible covariates, such as environmental and infectious exposures and family histories of atopy, asthma or respiratory disease.

Physician Office Records Assessment of Wheezing and Outpatient Pulmonary Morbidity Physician office charts will be reviewed to determine physical findings of wheezing, medication use and respiratory related hospitalization history. For primary care pediatricians, the family's consent authorizing release of medical information and an office contact questionnaire will be mailed or faxed to the provider. The questionnaire will be based on a similar document used by the Rochester Research Group to obtain medical information on respiratory issues. To help assure compliance with completing the questionnaire, a $25 honorarium will be offered to the office staff.

Data Collection: Ascertainment of Environmental and Genetic Covariates

Ascertainment of important environmental exposures and genetic risk factors that might confound the relationship between supplemental oxygen exposure and recurrent wheezing will be obtained along with the primary outcome during the same telephone and family interviews (Table 2). A second follow-on study to the SUPPORT Trial, not affiliated with the studies proposed here, is being independently proposed by other investigators to study specific genetic markers that predict greater risk of CLD. Although synergy between our study and the genetic study potentially exists, the genetic study is not yet funded and may not go forward.

Table 2. Postnatal and Genetic Covariates Evaluated as Potential Confounders of Oxygen and Wheezing

Covariates in Home Environment and Exposures The initial questionnaire and 6 month interviews will gather information on other *inhaled exposures* (tobacco, wood stoves, cold air), *residence* (urban vs. rural residence), *infectious exposures* (RSV, palivizumab) and medical risk factors (gastroesophageal reflux, congenital anatomic airway abnormalities)

Covariates in Family History Questionnaires will elicit *family history* of atopy (family history of asthma, eczema or allergy to foods, pets, molds, pollen or dust).

Data Collection: Ascertainment of Primary Exposure

Oxygen Exposure. In the SUPPORT Trial, it is assumed that managing infants with higher vs. lower targeted oxygen saturation range will result in different levels of supplemental oxygen exposure. Because oxygen is the primary exposure in the SUPPORT Follow-on Study and plays a central role in the disease model proposed, oxygen exposure will be quantified carefully. To document the difference in oxygen exposure between groups, FIO2 values will be recorded and analyzed as described in the SUPPORT Trial.

G.5 Sample size estimate with some statistical support based upon primary outcome

The SUPPORT Trial anticipates enrollment of 1506 patients < 28 weeks' gestation, providing 80% power to detect a 10% difference between treatment groups in the incidence of death/CLD and death/stage III Retinopathy of Prematurity (ROP). Assuming mortality of 35% for infants < 1000 grams (NICHD 2002 data), 978 infants would be expected to survive and be eligible for the SUPPORT follow-on study.

Power for detecting a difference between the high vs. low saturation groups for the primary outcome, recurrent wheezing We expect the prevalence of wheezing to be about 0.17 in the low saturation group, and about 0.31 in the high saturation group(12). For the power calculations, we also consider a scenario with a smaller difference between groups: 0.19 for the low saturation group and 0.29 for the high saturation group. We expect the follow up rate to be about 75%, which would result in data on about 733 patients. We also consider a lower follow up rate of 65%, which would result in about 635 patients. Power to detect a difference between groups based on a chi-square test with type I error alpha set at 0.05 is given in Table 7 for each scenario. From those results, we expect to have more than 80% power for the primary outcome. Also of interest are subgroup analyses, where we look separately at the CLD and non-CLD subjects. Of survivors, we expect 37% or 362 infants to have CLD. For the CLD group, we expect the prevalence of wheezing to be about 0.5 in the high saturation group and 0.3 in the low saturation group. If there is a 75% follow up rate, we will have 92% power to detect a difference between the two groups. For the non-CLD subgroup, we expect the prevalence to be 0.2 and 0.1 in the high and low groups, respectively. With 75% follow up, we will have 85% power. Thus, we expect to have adequate power for the primary outcome even in the analyses stratified by CLD.

Table 3. Power for primary outcome, recurrent wheezing.

Follow up rate	Low Saturation	High Saturation	power
75%	0.17	0.31	0.99
75%	0.19	0.29	0.88
65%	0.17	0.31	0.98
65%	0.19	0.29	0.84

We expect the study to be adequately powered for analysis of important secondary outcomes such as use of pulmonary medications. Based on results reported in Davis et al. for infants less than 27 weeks' gestational age [22], we expect the prevalence rate of pulmonary medications to be 0.42 in the high saturation group, and 0.19 in the lower saturation group. In that case, even with a 65% follow up rate, we would have more than 99% power to detect a difference between the groups with a chi-square test. Similarly, the CLD subgroup analyses would have more than 80% power under those assumptions. Based on the power numbers above, we could potentially enroll fewer subjects in the trial and still have adequate power. However, we choose to over enroll slightly to make up for the fact that some patients will likely be lost to follow up.

Data Analysis.

Analysis of primary dichotomous outcomes will be performed by chi square test and presented as a relative risk for development of that outcome. Number of outpatient pulmonary visits for respiratory illnesses will be presented as median values. The Wilcoxon Rank Sum test, a non-parametric alternative to the two-sample t-test, will be used to test for differences between the two groups. Statistical analyses will need to consider the effect of multiple comparison groups on the level of statistical significance. All analyses will be performed in conjunction with the Research Triangle Institute (RTI, North Carolina), the biostatistical support group for the NICHD Neonatal Network. Data will be presented as shown in tables 4-5. Mean FIO2 values in the high and low SpO2 groups will be compared by two sample t-test. Secondary analyses will be done to evaluate the effect of ventilator strategy on pulmonary outcome and presented similarly to table 4 and 5.

Table 4. ***Primary Dichotomous Outcomes***	**Low Saturation**	**High Saturation**	**RR**	**CI**	**p-value**
Parental Report of Recurrent Wheezing (%)					
Physician Diagnosed Recurrent Wheezing (%)					
Need for Outpatient Pulmonary Medications (%)					
Need for Physician Visit for Respiratory Illness (%)					
Need for Re-hospitalization for Respiratory Illness (%)					

Table 5. ***Primary Outcomes – Continuous Outcomes***	**Low Saturation**	**High Saturation**	**p-value**
Number of Physician Visit for Respiratory Illness (Median)			
Number of Emergency Visits for Respiratory Illness (Median)			
Number of Re-hospitalization for Respiratory Illness (Median)			

Expected Results We predict that premature infants managed with a lower targeted oxygen saturation range compared to those managed with a higher targeted oxygen saturation are exposed to lower levels of supplemental oxygen and have reduced risk of recurrent wheezing in the first 18-22 months' CA.

Anticipated Problems and Solutions

1) Participant attrition. As seen in the sample size calculation, the potential for patients to be lost to follow up over time will be offset by over enrolling patients to participate in the follow up. Because patients who enroll in the SUPPORT Trial are randomized, there should be no systematic bias favoring one group over another among patients who are lost to follow up. However, if loss to follow up is in part caused by the treatment or outcomes, this could bias the results. We will therefore investigate whether there are differences in key variables for subjects who are lost to follow up compared to those who remain in the study. For example, we will test whether subjects in one treatment arm were more likely to be lost to follow up than in the other arm. Similarly, we will compare wheezing rates at 6 months' for those who are later lost to follow up compared to those who remain in the study. We do not expect to see any major differences.
2) Low office respiratory health questionnaire response rate. For primary care offices that do not respond to the first mailing, a repeat questionnaire will be mailed. A phone call to the office will be made if there is no response to the second mailing. A $25 honorarium will also be offered to encourage replies.

3) The SUPPORT Follow-on Study of Pulmonary Outcomes has been prepared as the central project for Dr. Stevens' Patient Oriented Clinical Research Grant (K23 Award), submitted 10/1/04. If approved, funds from the K23 will be available to offset a portion of the cost of conducting this SUPPORT Trial Follow-on study. In the event that the K23 is not funded, I will seek additional funding from alternative sources including The American Lung Association and The March of Dimes Foundation.

G.6 Available population/compatibility with other ongoing protocols

Another secondary study proposed by a group independent from ours is looking at the genetics of reactive airways disease in patients enrolled in the SUPPORT Trial. The follow on study proposed here should be complementary to the genetics study, enhancing the both the quality and quantity of data on the prevalence of wheezing and need for outpatient pulmonary care in patients enrolled in the SUPPORT Trial.

G.7 Estimate of projected recruitment time

The recruitment time will be that of the SUPPORT Trial with a 18-22 month period of follow up to ascertain primary and secondary outcomes.

H. RISKS/BENEFITS, WITH ESTIMATE OF FREQUENCY/SEVERITY OF RISKS.

By using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care may be quantified, allowing assessment of whether infants who develop CLD and those who do not have improved pulmonary health as a result of the study intervention. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the follow up visit. We anticipate no risk to the patient of this observational follow on study.

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Center Costs **One Time Costs per Center**	**Hours**	**Cost/center ($43/hour)**	**# Centers**	**Rochester Costs $25/hr***	**Capitation/pt**	**Patients**	**NICHD Network Centers** Portion of Total Cost 1st year**	**NICHD Network Centers** Portion of Total Cost 4 years**	**Rochester** Portion of Total Cost 1st year**	**Rochester** Portion of Total Cost 4 years**	**Total Cost for the Entire Study^^**
RSRB	5	$215	16				$3,440				**$3,440**
Annual Costs Per Center											
RSRB renewal	2	$86	16					$1,376			**$1,376**
SubTotal (Direct Center Costs)							**$3,440**	**$1,376**			**$4,816**
Capitation Costs											
Cost per Infant											
Capitation											
Interview 1 - Conducted by coordinators at NICHD centers prior to discharge	0.5	$43			$22	700		$15,050		$0	**$15,050**
Interview 2 - Telephone interview from Rochester	2			$25	$50	700		$15,000		$20,000	**$35,000**
Interview 3 - Telephone interview from Rochester	2			$25	$50	700		$15,000		$20,000	**$35,000**
Interview 4 - Telephone interview from Rochester	2			$25	$50	700		$15,000		$20,000	**$35,000**
Telephone Charges (Long distance charges)										$2,000	**$2,000**
SubTotal Directs (Interviews)								**$60,050**		**$62,000**	**$122,050**
Outpatient Office Chart Review				$25		700		$17,500		$0	**$17,500**
Postage								$0		$500	**$500**
SubTotal Directs (Chart Reviews)								**$17,500**		**$500**	**$18,000**
Sub Total Directs (Yearly Interval)							**$3,440**	**$78,926**		**$62,500**	**$144,866**
Grand Total Directs (Network and Rochester)								***$82,366***		***$62,500***	***$144,866***

*assumes 35,000/year with 29% benefits, working 2000 hours per year

Legend

** Total costs shared between NICHD and Rochester (assuming Dr. Stevens' K23 Patient Oriented Research award is funded, submitted 10/1/04)

^^ Total cost born by NICHD Neonatal Research Network (if Dr. Stevens' K23 Award is not funded)

Budget Justification

Principal Investigator

Dr. Timothy P. Stevens, MD
Assistant Professor of Pediatrics
Dr. Stevens is a junior investigator. Using the SUPPORT Follow-on Pulmonary Outcome Study described here, Dr. Stevens submitted a Patient Oriented Clinical Research (K23) Grant application to the NICHD on 10/1/04. If funded, a portion of the funds from this K23 award (approximately $62,500) will be used to offset the SUPPORT Trial Pulmonary Outcome Follow-on Study (no salary requested for Dr. Stevens).

Co-Investigators

Dale Phelps, MD, Professor of Pediatrics, Center PI of the NICHD Neonatal Network in Rochester, NY will serve as a co-mentor for Dr. Stevens' K23 award. She will provide specific mentorship in clinical research study design and implementation. Dr. Phelps has extensive experience multi-center trials, including longitudinal follow up of infants enrolled in multi-centered trials. As the NICHD Neonatal Research Network Site Principal Investigator, she will act as a liaison and advocate for Dr. Stevens in the NICHD Neonatal Network (no salary requested).

Peter Szilagyi, MD, MPH, Professor of Pediatrics, Division Chief, General Pediatrics, University of Rochester, will provide senior mentorship of Dr. Stevens' K23 research projects as well his didactic coursework and training in clinical research during the period of the K23 award. He will supervise the clinical research projects. Dr. Szilagyi has distinguished himself in health services research and health outcomes and as a mentor for other clinical researchers. Dr. Szilagyi is the 2002 recipient of the Ambulatory Pediatric Association's Lifetime Research Award, the single highest research honor among general academic pediatricians (no salary requested).

Jonathan Klein, MD, MPH, Associate Professor of Pediatrics and of Community and Preventive Medicine, Director, Health Services Research Group will serve as a co-mentor. Dr. Klein is one of the leading child and adolescent health services researchers in the US. His experience in adolescent medicine and health services research includes studies on adolescent reproductive health care, adolescents' access to care and preferences for care, implementation of preventive services, and studies on the reliability and validity of adolescent report of health behavior and health service use. Dr. Klein is a member of the US Preventive Services Task Force, and is Chair of the American Academy of Pediatrics Committee on Adolescence. Dr. Klein will supervise and mentor Dr. Stevens in the fieldwork necessary to complete this study, including implementation of the telephone follow-up surveys, follow-up design, and data preparation (no salary requested).

Consultants

Neil Finer, MD, Professor of Pediatrics, Vice-Chair of Pediatrics, University of Cal San Diego will serve as a consultant to the SUPPORT Trial Follow On Study that is presented in Specific Aim 1 of this proposal. As National PI for the SUPPORT Trial, Dr. Finer will oversee the primary randomized trial. He will consult on design, implementation, and analysis of the SUPPORT Follow-on Study (no salary requested).

Technical Staff

Caryn Graff-Haven, MPH, MBA, Project Manager, HSR Group. Ms. Graff-Haven is a Senior Health Project Coordinator at the University of Rochester. She will help design and manage development of survey protocols, data entry and cleaning, coordinate and oversee all data acquisition and management activities, and maintain communication between collaborating sites and U of R investigators and staff. Support requested as part of the hourly rate on the budget page.

TBN, Information Analyst. A full time information analyst will be hired to conduct interviews and data entry for the numerous interviews proposed for this project. This will allow for maximal continuity between interviewers and subjects, and will promote adherence to follow-up protocols. Support requested as part of the hourly rate on the budget page.

Student research assistants. Part time student research assistants will conduct interviews and assist with data entry, in particular during the peak enrollment/follow-up time. Support requested as part of the hourly rate on the budget page.

Supplies

General Supplies

$1,200/year is requested each year for supplies, telephone and fax costs, and for photocopying of materials for project meetings.

Other Expenses

Research Subject Review Board Costs – A total of $4,816 is requested to fund a separate informed consent for the follow-on study.

$2,000 is requested for long distance telephone charges to conduct the telephone surveys from Rochester

$17,500 is requested for honoraria to pediatric office staff to complete outpatient chart review.

$500 is requested for stationary, envelopes and postage for mailing outpatient chart review honoraria.

SUPPORT FOLLOW-ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED AT TIME OF ENROLLMENT
PRIOR TO NICU DISCHARGE

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

QUESTIONNAIRE: ENROLLED CHILD
(Nurse Administered)

Child's Name: _____ Date: ____/____/____
Mo. Day Yr.

Child's Sex 1. Male 2. Female

Child's Birthdate ____/____/____ Apgar ____/____
Mo. Day Yr.

Person being interviewed:

1. Child's Mother
2. Child's Father
3. Both Parents
4. Child's female guardian
5. Child's male guardian
6. Other woman (SPECIFY RELATIONSHIP) _____
7. Other man (SPECIFY RELATIONSHIP) _____

1. At this time, we would like a little information about the environment in which your new child will grow up. First, how many people live with you in your home?

Total household members: _____

2a. After the first few months, will your child be sharing a room with other family members on a regular basis?

1. Yes
2. No

2b. IF YES: How many people will sleep in the same room with him/her? _____

2c. How many living areas are there in your house, excluding closets and bathrooms?_____

3. How many pets are there in the household, either kept inside or out? (RECORD THE NUMBER OF EACH LIVING IN AND OUT OF THE HOUSE).

	Number Kept Inside	Number Kept Outside
Dogs	_____	_____

Cats	_____	_____
Gerbils, Hamsters and Guinea Pigs	_____	_____
Other (Please specify type)		
_____	_____	_____
_____	_____	_____

4. On a scale of 1 to 5, where 1 is not dusty and 5 is very dusty, how dusty would you say your home is compared to other homes in your neighborhood? (CIRCLE APPROPRIATE NUMBER).

Not at all Dusty — Very Dusty

5. Does your home or apartment have air conditioning or some kind of cooling?
   1. Air Conditioning
   2. Evaporative Cooling
   3. Both
   4. None
   5. Other _____
   6. Don't Know

6. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).
   1. Steam or hot water (radiator)
   2. Central gas furnace (furnace)
   3. Electric
   4. Wood Stove
   5. Other
   6. Don't know

7. What fuel is used most for cooking in your home?
   1. Electricity
   2. Gas
   3. Fuel Oil
   4. Wood Stove
   5. Other
   6. Don't Know

8a. Is your child being breast fed? 1. Yes 2. No...SKIP TO QUESTION 9

IF YES,

b. Will this be supplemented with formula? 1. Yes 2. No

c. When do you think the supplement will begin? _____months

d. Do not know when supplements will begin. 1. Yes 2. No

9. Does the mother plan to work outside the home within the next year?
   1. Yes
   2. No
   3. Don't Know

10a. Will your child be cared for by anyone who is not an immediate family member for a major part of the next year?
   1. Yes
   2. No
   3. Maybe

IF YES or MAYBE to 10a:

b. Where will this care be provided?
   1. The parent or guardian's home?
   2. Home of a relative or private sitter?
   3. Day care setting (non-private) ?
   4. Don't Know

c. Will this involve other children, not counting the child's brothers and sisters?
   1. Yes
   2. No

12. Finally, which relative is most likely to have your address in case we lose contact with you?

_____ _____
Name Relationship

_____
Address

_____

SUPPORT FOLLOW ON STUDY

FAMILY HISTORY / FAMILY CONTACT QUESTIONNAIRE - ADMINISTERED PRIOR TO NICU DISCHARGE

1. Name:				
2. Relationship to enrolled child:	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact	1. Mother 2. Father 3. Maternal Grandmother 4. Maternal Grandfather 5. Paternal Grandmother 6. Paternal Grandfather 7. Sibling 8. Non-relative contact
3. Age (in years):	________	________	________	________
4. Sex:	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female	1. Male 2. Female
5. Does this person currently have:	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
a. Bronchitis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
b. Emphysema?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
c. Bronchiectasis?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
d. Asthma?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
e. Inhaled Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
f. Food Allergies?	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No	1. Yes 2. No
g. Any other chronic respiratory disease? (SPECIFY)	________ ________	________ ________	________ ________	________ ________
6. How often does this person smoke in the house?	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently	1. Never 2. Rarely 3. Sometimes 4. Frequently

SUPPORT FOLLOW ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED BY TELEPHONE AT 6 AND 12 MONTHS CORRECTED AGE

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Before we begin this interview it would be helpful if you could gather any medications your child has been prescribed or has been taking and have them in front of you. Can you do that now or is there a better time to call you?

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing concerns your child may have.

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

4a. Has his/her chest ever sounded wheezy or whistling?
   3. Yes
   4. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?

1	2	3	4	5
Very rarely				On Most days

e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing ~

g. Has this child's wheezing/whistling occurred as attacks?
   1. Yes
   2. No

h. Has this child ever been awakened at night by wheeze or by shortness of breath?
   1. Yes
   2. No

i. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

j. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES. BE SURE TO COMPLETE QUESTIONS 24 AND 25

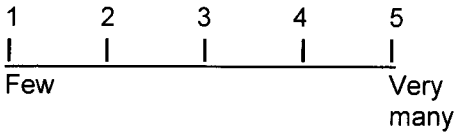
5. Does this child's chest sound wheezy or whistling during or shortly after vigorous exercise or crying?
   1. Yes, usually
   2. Yes, occasionally
   3. No

6a. Has he/she ever had episodes of shortness of breath or chest tightness?
   1. Yes
   2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6A:

b. Has this ever occurred when the child is at rest?
   1. Yes
   2. No

c. During the past year, how many episodes did he/she have?



d. How old was this child when he/she had the first such episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

OR: check here if the child still has condition: ~

f. Has the child's chest ever sounded wheezy or whistling during episodes of shortness of breath or chest tightness?
   1. Yes
   2. No

g. Has he/she ever seen a doctor for shortness of breath or chest tightness?
   1. Yes
   2. No

h. Has this child ever taken any medicine for shortness of breath?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

7. Has this child ever had a cough when he/she did not have a cold?
   1. Yes
   2. No . . . SKIP TO QUESTION 6

IF **YES** TO QUESTION 5a

b. At what time of the day has this cough usually occurred? (CIRCLE ALL THAT APPLY) 1.
   1. In the morning, shortly after rising
   2. Later in the day
   3. During the night
   4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?
   1. Yes
   2. No

d. How often has this child been bothered by coughing?

1	2	3	4	5
Very Rarely				On most days

e. How old was the child when he/she first began to cough?
   ____ months

   OR: check here if child is still coughing: _

f. How old was this child when he/she stopped coughing?
   _____ months

g. Has the cough usually been dry or loose?
   1. Dry
   2. Loose

h. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?
   1. Yes
   2. No

i. How often has your child raised phlegm, sputum or mucus when coughing?
   1. Never
   2. Occasionally
   3. Often

j. Has he/she ever seen a doctor about the cough?
   1. Yes
   2. No

Does this child cough during or shortly after vigorous exercise?
   1. Yes, usually
   2. Yes, occasionally
   3. No

8a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 9a

IF **YES** TO QUESTION 8A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: ~

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ _ months

OR: check here if doctor never said he/she had asthma: ~

e. **During the past year**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past year**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

9a. Has your child ever had bronchitis?

1. Yes
2. No . . . SKIP TO QUESTION 10a

IF **YES** TO QUESTION 9a:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last episode occurred?

_____ months

OR: check here if child still has bronchitis ___

d. How old was this child when you were first told by a doctor that he/she had bronchitis?

_____ months

OR: check here if doctor never said he/she had bronchitis___

e. How often has this child had bronchitis?

1. one episode only
2. 2-3 episodes
3. 4 or more separate episodes
4. almost constantly

f. During the past year, how much trouble did he/she have with bronchitis?

1 2 3 4 5

None A great deal

g. During the past year, did this child take any medicine for bronchitis?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 254

10a. Has your child ever had croup?

1. Yes
2. No . . . SKIP TO QUESTION 11a

IF **YES** TO QUESTION 10a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of croup?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

11a. Has your child ever had bronchiolitis, or any wheezing illness in the first year of life not due to asthma?

1. Yes
2. No . . . SKIP TO QUESTION 12a

IF **YES** TO QUESTION 11A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

12a. Has your child **ever** had pneumonia?

1. Yes
2. No . . . SKIP TO QUESTION 13

IF **YES** TO QUESTION 12a:

b. Was this diagnosed by a doctor?
1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?
1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

13a. Was this child breast fed?

1. Yes
2. No . . . SKIP TO QUESTION 14

IF **YES** TO QUESTION 13a:

b. For how many months was this child breast fed?
1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

14a. Has the mother smoked at all since this child was born?

1. Yes
2. No . . . SKIP TO QUESTION 15a

IF **YES** TO QUESTION 14a:

b. For how many months did the mother smoke since this child was born?
_____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES)

_____ cigarettes
_____ pipes
_____cigars
_____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?
Never
Occasionally
Frequently

15a. Has the father smoked at all since the child was born?

1. Yes
2. No . . . SKIP TO QUESTION 16

IF **YES** TO QUESTION 15a:

b. For how many months did the father smoke since this child's birth?

_____ months

c. On the average, how many of each of the following did he smoke per day during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES).

_____ cigarettes
_____ pipes
_____ cigars
_____ non-tobacco cigarettes

d. How often has the father smoked in the same room with this child?

1. Never
2. Occasionally
3. Frequently

16. Did any other household member regularly smoke in the house since this child's birth?

1. Yes
2. No

17. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

18. How many brothers and sisters (including half siblings) does this child have?

_____

19a. Are there any other children living in your household **besides** this child and all of his/her siblings?

1. Yes
2. No . . . SKIP TO QUESTION 20

IF **YES** TO QUESTION 19a:

b. How many children other than this child and his/her siblings live in your house?

_____

20. Do you have any pets?

1. Yes
2. No

1❑ Dogs #:_____
2❑ Cats #: _____
3❑ Other #:_____

21. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).

1. steam or hot water
2. central gas furnace
3. wall or floor gas furnace
4. electric
5. other
6. don't know

OUTPATIENT RESPIRATORY PROPHYLAXIS

22. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?

1. Yes
2. No

23. Did this child receive a flu shot?

1. Yes
2. No

OUTPATIENT RESPIRATORY SUPPORT

24a. Is your child on any oxygen therapy (oxygen tank at home)?

1. Yes
2. No

IF **YES** TO QUESTION 24a:

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

*lpm = liters per minute

25. Is your child taking any medicines for asthma or wheezing?

1. Yes
2. No
3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as:* ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other _____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

THANK YOU FOR YOUR COOPERATION

SUPPORT FOLLOW ON STUDY
OUTPATIENT RESPIRATORY OUTCOMES

ADMINISTERED AT 18-22 MONTH FOLLOW UP VISIT

This questionnaire should be completed by the parent for:

_____

All questions pertain only to his/her health.

The questions can be answered by circling the number of the best answer or by filling in a blank with a number or word.

Example: Do you live in the United States?

(1) Yes
2. No

Please answer all questions as accurately as possible. If you desire help in answering a question, please put a checkmark (√) in front of the question number.

As with all information we collect, the answers to these questions will be kept confidential.

Thank you for your cooperation in providing us with this important information, and for your continued participation in the Children's Respiratory Study.

TODAY'S DATE: ___ / ___ / ___
Mo. Day Yr.

PLEASE CONFIRM PERSONAL INFORMATION AND MAKE NECESSARY CORRECTIONS.

Child's name _____

DOB ___ / ___ / ___
Mo. Day Yr.

Telephone Number _____-_____-_____

Address _____

_____

****

1. Pediatrician Name _____

Telephone Number _____-_____-_____

Address _____

_____

Interview begins:
Some of these questions will be familiar to you. Since we last spoke (***XX*** months ago) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing concerns your child may have.

2. Since our last contact with you about your child, how many times has your child....

2a Needed a visit to the doctor's office or emergency department because of wheezing or breathing problems?

_____ times What was the date of that visit?
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____
Location_____ Date _____/_____/_____

2b How many times has your child needed to stay in the hospital overnight because of wheezing, trouble breathing, or asthma symptoms?

_____ times What was the location and date that your child was in the hospital?
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____
Location _____ from: ____/_____/_____ to: _____/_____/_____

3. Has your child had any respiratory symptoms since discharge from the NICU?
   1. Yes
   2. No

4a. Has his/her chest ever sounded wheezy or whistling?
   1. Yes
   2. No . . . SKIP TO QUESTION 5

IF **YES** TO QUESTION 4a:

b. Has this occurred with colds?
   1. Yes
   2. No

c. Has this child's chest ever sounded wheezy or whistling apart from colds?
   1. Yes
   2. No

d. How often has this child had the wheezing or whistling?

1	2	3	4	5
Very rarely				On Most days

e. How old was this child when his/her chest first sounded wheezy or whistling?
   _____ months

f. At what age did he/she stop wheezing or whistling?

   _____ months

   OR: check her if child is still wheezing _

g. Has this child's wheezing/whistling occurred as attacks?
   1. Yes
   2. No

h. Has this child ever been awakened at night by wheeze or by shortness of breath?
   1. Yes
   2. No

i. Has he/she ever seen a doctor about the wheeze?
   1. Yes
   2. No

j. Has this child ever taken any medicine for wheeze?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

5. Does this child's chest sound wheezy or whistling during or shortly after vigorous exercise or crying?
   1. Yes, usually
   2. Yes, occasionally
   3. No

6a. Has he/she ever had episodes of shortness of breath or chest tightness?
   1. Yes
   2. No . . . SKIP TO QUESTION 7

IF **YES** TO QUESTION 6A:

b. Has this ever occurred when the child is at rest?
   1. Yes
   2. No

c. During the past year, how many episodes did he/she have?

1 2 3 4 5
Few — Very many

d. How old was this child when he/she had the first such episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

OR: check here if the child still has condition: _

f. Has the child's chest ever sounded wheezy or whistling during episodes of shortness of breath or chest tightness?
   1. Yes
   2. No

g. Has he/she ever seen a doctor for shortness of breath or chest tightness?
   1. Yes
   2. No

h. Has this child ever taken any medicine for shortness of breath?
   1. Yes, prescribed by doctor
   2. Yes, not prescribed by doctor
   3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

7. Has this child ever had a cough when he/she did not have a cold?
   1. Yes
   2. No . . . SKIP TO QUESTION 6

IF **YES** TO QUESTION 5a

b. At what time of the day has this cough usually occurred? (CIRCLE ALL THAT APPLY)
   1.
   1. In the morning, shortly after rising
   2. Later in the day
   3. During the night
   4. No relation to time of day

c. Has he/she ever coughed on most days for as much as 2 to 3 months per year?
   1. Yes
   2. No

d. How often has this child been bothered by coughing?

1	2	3	4	5
Very Rarely				On most days

e. How old was the child when he/she first began to cough?
   ____ months

   OR: check here if child is still coughing: _

f. How old was this child when he/she stopped coughing?
   _____ months

g. Has the cough usually been dry or loose?
   1. Dry
   2. Loose

h. Has this child's chest ever sounded wheezy or whistling with episodes of coughing?
   1. Yes
   2. No

i. How often has your child raised phlegm, sputum or mucus when coughing?
   1. Never
   2. Occasionally
   3. Often

j. Has he/she ever seen a doctor about the cough?
   1. Yes
   2. No

Does this child cough during or shortly after vigorous exercise?
   1. Yes, usually
   2. Yes, occasionally
   3. No

8a. Has your child ever had asthma (reactive airways disease)?

1. Yes
2. No . . . SKIP TO QUESTION 9a

IF **YES** TO QUESTION 8A:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last attack occurred?

_____ months

OR: check here if child still has asthma: _

d. How old was this child when you were first told by a doctor that he/she had asthma?

_____ _ months

OR: check here if doctor never said he/she had asthma: _

e. **During the past year**, how many asthma attacks did he/she have?

1. No attacks
2. A few (1-3) attacks
3. Several (4-12) attacks
4. Many (13 or more) attacks
5. Attacks almost every day

f. **During the past year**, did this child take any medicine for asthma?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 25

9a. Has your child ever had bronchitis?

1. Yes
2. No . . . SKIP TO QUESTION 10a

IF **YES** TO QUESTION 9a:

b. How old was this child when the symptoms first began?

_____ months

c. How old was he/she when the last episode occurred?

_____ months

OR: check here if child still has bronchitis ___

d. How old was this child when you were first told by a doctor that he/she had bronchitis?

_____ months

OR: check here if doctor never said he/she had bronchitis___

e. How often has this child had bronchitis?

1. one episode only
2. 2-3 episodes
3. 4 or more separate episodes
4. almost constantly

f. During the past year, how much trouble did he/she have with bronchitis?

1 2 3 4 5

None A great deal

g. During the past year, did this child take any medicine for bronchitis?

1. Yes, prescribed by a doctor
2. Yes, not prescribed by a doctor
3. No

IF YES, BE SURE TO COMPLETE QUESTIONS 24 AND 254

10a. Has your child ever had croup?

1. Yes
2. No . . . SKIP TO QUESTION 11a

IF **YES** TO QUESTION 10a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of croup?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

11a. Has your child ever had bronchiolitis, or any wheezing illness in the first year of life not due to asthma?

1. Yes
2. No . . . SKIP TO QUESTION 12a

IF **YES** TO QUESTION 11A

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of bronchiolitis?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

12a. Has your child **ever** had pneumonia?

1. Yes
2. No . . . SKIP TO QUESTION 13

IF **YES** TO QUESTION 12a:

b. Was this diagnosed by a doctor?

1. Yes
2. No

c. Did the child have one or more episodes of pneumonia?

1. One episode
2. More than one episode

d. At what age did the child have the first episode?

_____ months

e. How old was this child when he/she had the last such episode?

_____ months

13a. Was this child breast fed?

1. Yes
2. No . . . SKIP TO QUESTION 14

IF **YES** TO QUESTION 13a:

b. For how many months was this child breast fed?

1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

14a. Has the mother smoked at all since this child was born?

1. Yes
2. No . . . SKIP TO QUESTION 15a

IF **YES** TO QUESTION 14a:

b. For how many months did the mother smoke since this child was born?

_____ months

c. On the average, how many of **each** of the following did she smoke **per day** during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES)

_____ cigarettes
_____ pipes
_____cigars
_____non-tobacco cigarettes

d. How often has the mother smoked in the same room with this child?

Never
Occasionally
Frequently

15a. Has the father smoked at all since the child was born?

1. Yes
2. No . . . SKIP TO QUESTION 16

IF **YES** TO QUESTION 15a:

b. For how many months did the father smoke since this child's birth?

_____ months

c. On the average, how many of each of the following did he smoke per day during that time? (NOTE: ONE PACK CONTAINS 20 CIGARETTES).

_____ cigarettes
_____ pipes
_____ cigars
_____ non-tobacco cigarettes

d. How often has the father smoked in the same room with this child?

1. Never
2. Occasionally
3. Frequently

16. Did any other household member regularly smoke in the house since this child's birth?

1. Yes
2. No

17. Does this child spend 9 or more hours per week in the company of other children (not including his or her brothers and sisters) such as at a babysitter's home or day care?

1. Yes
2. No

18. How many brothers and sisters (including half siblings) does this child have?

_____

19a. Are there any other children living in your household **besides** this child and all of his/her siblings?

1. Yes
2. No . . . SKIP TO QUESTION 20

IF **YES** TO QUESTION 19a:

b. How many children other than this child and his/her siblings live in your house?

_____

20. Do you have any pets?
1. Yes
2. No

1❑ Dogs #:_____
2❑ Cats #: _____
3❑ Other #:_____

21. How is your home heated? (IF MORE THAN ONE, PLEASE CIRCLE ALL TYPES).

1. steam or hot water
2. central gas furnace
3. wall or floor gas furnace
4. electric
5. other
6. don't know

OUTPATIENT RESPIRATORY PROPHYLAXIS

22. Did this child receive palivizumab to prevent Respiratory Syncytial Virus (Synagis, RSV shot)?
1. Yes
2. No

23. Did this child receive a flu shot?
1. Yes
2. No

OUTPATIENT RESPIRATORY SUPPORT

24a. Was your child ever on any oxygen therapy (oxygen tank at home)?

1. Yes
2. No

IF **YES** TO QUESTION 24a:

b. Oxygen cannula FiO2_____ lpm*_____
c. Oxygen hood FiO2_____ lpm*_____
d. Ventilator FiO2_____ lpm*_____

*lpm = liters per minute

25. Is your child taking any medicines for asthma or wheezing?

1. Yes
2. No
3. Not sure

Interviewer - If yes, please check the box next to EACH medicine that this child is currently taking for asthma and check how often it is taken. If a child takes multiple medicines from one category, indicate the greatest frequency with which any one medicine from that category is taken.

Medicine	How OFTEN is it taken?
a. *Rescue medicine such as*: ❑ Albuterol ❑ Proventil ❑ Ventolin ❑ Xopenex ❑ Serevent ❑ Volmax ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
b. *Inhaled medications such as:* ❑ Cromolyn (Intal) ❑ Nedocromil (Tilade) ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
c. *Inhaled steriods such as:* ❑ Flovent ❑ Advair ❑ Vanceril ❑ Beclovent ❑ Azmacort ❑ Aerobid ❑ Pulmicort ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
d. *Systemic steriods such as:* ❑ Prednisone ❑ Decadron ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
e. *Leukotriene blocker such as:* ❑ Accolate ❑ Singulair ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
f. *Methylxanthines such as:* ❑ Theophylline ❑ Other_____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick
g. *Diuretic medications such as:* ❑ Lasix ❑ Diuril ❑ Other _____	1❑ Everyday 2❑ Sometimes 3❑ Only when Sick

ATOPY HISTORY

26. **During the past year**, for how many days has this child been unable to do his/her usual activities because of illnesses such as chest (not head) colds, bronchitis, asthma or pneumonia?

_____ days

27. How many head colds (common colds) **per year** does this child usually have?

1. Few (0-3 per year)
2. Some (4-5 per year)
3. Frequent (6-9 per year)
4. Constant (more than 9 per year)

28a. Has your child **ever** had hay fever or any other condition that makes his/her nose runny, stuffy, or itchy **apart** from colds?

1. Yes
2. No . . . SKIP TO QUESTION 29

IF **YES** TO QUESTION 28a:

b. How old was your child when you first noticed this condition?

_____ months

c. How old was this child when he/she stopped having this condition?

_____ months

OR: check here if child still has condition ~

d. When this child has the runny or stuffy nose, does he/she also usually:

Cough?	1. Yes 2. No
Wheeze?	1. Yes 2. No
Have shortness of breath?	1. Yes 2. No

29. Has this child **ever** had allergies which cause nose, eye or lung problems?

1. Yes
2. No

30. Has a doctor **ever** told you that this child had sinus trouble?

1. Yes
2. No

31a. Has this child **ever** been allergic to any food?

1. Yes
2. No

b. Has he/she **ever** been allergic to any medicine?

1. Yes
2. No

32a. Has this child **ever** had eczema (allergic skin rash)?

1. Yes

2. No . . . SKIP TO QUESTION 33a

IF **YES** TO QUESTION 32A:

b. Has a doctor told you this child had eczema?
1. Yes
2. No

c. At what age did the eczema begin?
_____ months

d. How old was this child when he/she last had eczema?
_____ months

OR: check here if child still has eczema ~

33a. Was this child breast fed?
1. Yes
2. No . . . SKIP TO QUESTION 34

IF **YES** TO QUESTION 33a:

b. For how many months was this child breast fed?
1. Less than 1 month
2. 1-3 months
3. 4-6 months
4. more than 6 months

34. At what age was formula introduced?
1. Never
2. less than 1 month
3. 1-3 months
4. 4-6 months
5. more than 6 months

35. At what age was cow's milk (nonformula) started?
1. Never
2. Less than 1 month
3. 1-3 months
4. 4-6 months
5. 7-9 months
6. 9-11 months
7. 12 or more months

36. At what age did he/she begin to receive table foods?
1. less than 1 month
2. 1-3 months
3. 4-6 months
4. 7-9 months
5. more than 9 months

THANK YOU FOR YOUR COOPERATION

From: Higgins, Rosemary (NIH/NICHD)
To: Hastings, Betty J.
Subject: RE: SUPPORT
Date: Friday, January 07, 2005 8:41:00 AM

I think it is a clarification also, rather than a revision

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Thursday, January 06, 2005 2:57 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT

Hi Rose,
I realize you are at a meeting but have a question I need to ask you. Wade told me about a change to MOP and the Protocol. It is a change to the extubation criteria which stated "An FiO2 <=.35 with a SpO2 >88% using the study pulse oximeters" and he wants to change it to >=88%. One of the sites thinks that this should be a protocol revision and thus will need to have IRB approval. What do you think? I talked to Ken about this but not sure that he agrees that it is a protocol revision (maybe more of a clarification).

Thanks.
Betty

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

From: Higgins, Rosemary (NIH/NICHD)
To: Petrie, Carolyn
Subject: RE: SUPPORT Trial Follow On Study of Pulmonary Outcomes
Date: Friday, January 07, 2005 8:41:00 AM

Send them an email asking for Yes/NO to go forward.
Thanks
Rose

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Thursday, January 06, 2005 2:48 PM
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT Trial Follow On Study of Pulmonary Outcomes

Rose-

I received no comments from the FU protocol review group on Dr. Steven's protocol.

Carolyn

-----Original Message-----
From: Petrie, Carolyn
Sent: Wednesday, November 24, 2004 11:08 AM
To: bvohr@wihri.org; yjohnson@med.wayne.edu; adusick@iupui.edu; gary_myers@urmc.rochester.edu; rdillard@wfubmc.edu; 'golds005@mc.duke.edu'; Myriam Peralta (MPeralta@PEDS.UAB.EDU)
Cc: aRose Higgins (higginsr@mail.nih.gov); Petrie, Carolyn
Subject: FW: SUPPORT Trial Follow On Study of Pulmonary Outcomes

Dear Follow UP Protocol Review-

Please review the attached materials regarding Dr. Stevens' follow up study on pulmonary outcomes and send me your written comments by **Monday, January 6th.**

Thank you very much and Happy Holidays!
Carolyn

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 24, 2004 8:57 AM
To: Petrie, Carolyn
Subject: FW: SUPPORT Trial Follow On Study of Pulmonary Outcomes

please send to FU review subcommittee.
Thanks
Rose
-----Original Message-----
From: Richard A. Ehrenkranz [mailto:richard.ehrenkranz@yale.edu]
Sent: Tuesday, November 23, 2004 5:08 PM
To: dale_phelps@urmc.rochester.edu; Jon.E.Tyson@uth.tmc.edu; poo@rti.org; moshea@wfubmc.edu; Higgins, Rosemary (NIH/NICHD); sshankar@med.wayne.edu
Cc: petrie@rti.org; adas@rti.org
Subject: Fwd: SUPPORT Trial Follow On Study of Pulmonary Outcomes

Hi:

I have attached Tim Stevens' response. We will also plan to discuss this revision on January 7th. Mike and Neil were the primary reviewers of the initial version. We will also forward this proposal to the Follow-up Protocol Review Subcommittee and hope to comments from them by our Jan 7th call.

Have a Happy Thanksgiving!
Richard

Date: Sat, 20 Nov 2004 14:49:16 -0500
From: "Stevens, Timothy" <Timothy_Stevens@URMC.Rochester.edu>
Subject: SUPPORT Trial Follow On Study of Pulmonary Outcomes
To: "'richard.ehrenkranz@yale.edu'" <richard.ehrenkranz@yale.edu>,
"'nfiner@ucsd.edu'" <nfiner@ucsd.edu>
Cc: "Phelps, Dale" <Dale_Phelps@URMC.Rochester.edu>
X-Mailer: Internet Mail Service (5.5.2657.72)
X-YaleITSMailFilter: Version 1.1e (attachment(s) not renamed)

Drs. Ehrenkranz and Finer,

Please delete the previous email and consider this version. I had inadvertently not saved the final edits before emailing the previous version to you.

Thanks

Tim

-----Original Message-----
From: Stevens, Timothy
Sent: Saturday, November 20, 2004 2:40 PM
To: 'richard.ehrenkranz@yale.edu'; 'nfiner@ucsd.edu'
Cc: Phelps, Dale
Subject: SUPPORT Trial Follow On Study of Pulmonary Outcomes

Drs. Ehrenkranz and Finer,

Thank you for your comments on our protocol. We have revised the protocol to address the concerns of the committee.

An important change in the protocol is the option of allowing each NICHD Network Center to

choose whether to administer the questionnaires locally (at their center) or to have the University of Rochester, Health Services Research (HSR) Group administer the questionnaires.

A second major consideration regards whether to treat death and adverse pulmonary outcome as competing outcomes. We agree with Dr. Higgins that treating death and pulmonary morbidity as competing outcomes is logical and appropriate. However, before making this change, we await your opinion as to whether the SUPPORT Consent Form can include consent for the Follow On Study. For the reasons outline in response #5, it is our opinion that if all patients enrolled in SUPPORT are also enrolled in the SUPPORT Follow On Study, then death and pulmonary morbidity directly compete. However, if not all survivors of SUPPORT are enrolled in the SUPPORT Follow On Study, then death and pulmonary morbidity do not directly compete. If the protocol committee agrees, we will gladly update the protocol to include death and adverse pulmonary outcome as competing outcomes.

We hope that our revised protocol can be discussed in the December teleconference. This will allow any further protocol revisions (especially the potential "competing outcome" revision) to be made in time for the January Steering Committee meeting.

A timely funding decision will allow the Follow On Study and the main trial to begin concurrently and will provide further support to my K23 award. I expect the K23 award to offset approximately $60,000 of the cost of the Follow On Study.

Attached please find the following:

1. Our responses the Protocol Committee's comments
2. Revised Protocol
3. Revised Outcome Questionnaires (Appendices A-C)

Thank you

Tim Stevens

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

From: Jon E Tyson
To: "Richard A. Ehrenkranz"; dale_phelps@urmc.rochester.edu; poo@rti.org; moshea@wfubmc.edu; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; sshankar@med.wayne.edu
Cc: petrie@rti.org
Subject: RE: Review SUPPORT DNA Registry
Date: Thursday, January 06, 2005 6:08:43 PM

Rich, as we discussed, I think it would be good if every Network protocol recommended by the Protocol Review Committee were reviewed prior to that recommendation by a clinical epidemiologist who had a formal association with the Network. Such a position exists in the MFM Network. As we discussed this person could bear other responsibilities, including review of the primary manuscript for every clinical trial. If such a position were created, I would think an epidemiologist experienced in neonatal trials would be desirable.

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

-----Original Message-----
From: Richard A. Ehrenkranz [mailto:richard.ehrenkranz@yale.edu]
Sent: Thursday, January 06, 2005 4:49 PM
To: dale_phelps@urmc.rochester.edu; Jon.E.Tyson@uth.tmc.edu; poo@rti.org; moshea@wfubmc.edu; nfiner@ucsd.edu; higginsr@mail.nih.gov; sshankar@med.wayne.edu
Cc: petrie@rti.org
Subject: Review SUPPORT DNA Registry

Hi:
Speak to you tomorrow.
Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

From:	Richard A. Ehrenkranz
To:	dale_phelps@urmc.rochester.edu; Jon.E.Tyson@uth.tmc.edu; poo@rti.org; moshea@wfubmc.edu; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; sshankar@med.wayne.edu
Cc:	petrie@rti.org
Subject:	Review SUPPORT DNA Registry
Date:	Thursday, January 06, 2005 5:49:31 PM
Attachments:	RAE-Review SUPPORT DNA registry 6Jan05.doc

Hi:
Speak to you tomorrow.
Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
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333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

January 6, 2005

Protocol: DNA Repository for SUPPORT Trial

Investigators: CM Cotton, MD and K Schibler, MD

Reviewer: Richard A. Ehrenkranz, MD

The investigators have responded to the suggestions of the Protocol Review Subcommittee and combined their earlier protocols, "Asthma-related Genes and Bronchopulmonary Dysplasia Risk" and "Surfactant Protein Genetic Polymorphisms and Severity of RDS," into a proposal to develop a prospective DNA sample bank for candidate gene association studies as a secondary to the Network's SUPPORT Trial.

The investigators propose that families would be approached for consent to allow use of an aliquot of cord blood or, in the absence of cord blood, collection of 50 microliters of blood on a filter paper card, for development of a prospective DNA repository that would allow study of the effects of genetic variation on the risk of diseases of ELBW infants. DNA extracted from the sample would be amplified and then stored at the Duke Center for Human Genetics.

Such a resource would provide DNA for candidate gene association studies from approximately 1,000 extremely premature infants, along with extensive clinical data and extensive follow-up for accurate phenotyping of neonatal morbidities. Such studies could lead to a better understanding of the pathophysiology of morbidities of extremely preterm infants, and could lead to improved prevention and treatment strategies for these diseases.

The investigators have provided an excellent rationale and justification for the establishment of this prospective DNA repository. However, they have proposed that Molecular Staging, Inc perform the DNA amplification. While I have previously supported such a plan, MSI was recently purchased by Qiagen, a German company that specializes in developing and marketing kits. It is unclear whether Qiagen will be willing to perform the DNA amplification on 3 mm punches from the cytokine filter paper blood spots and permit the creation of the Network's anonymized DNA repository, let alone commit to amplification of samples that have yet to be collected. Therefore, while I strongly favor developing a prospective DNA registry, perhaps the investigators should propose one sample format (blood aliquot, filter paper blood spot, or buccal smear) and propose that sample collection begin while the site that will perform the DNA amplification is identified.

From: Richard A. Ehrenkranz
To: cotte010@mc.duke.edu; kurt.schibler@cchmc.org
Cc: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: DNA Repository for SUPPORT
Date: Wednesday, January 05, 2005 4:05:47 PM

Hi:
The Protocol Review Subcommittee will be reviewing this protocol on Friday, January 7th. As one of the primary reviewers, I like this project, but have one major question. Now that Qiagen has purchased Molecular Staging, Inc, how will the DNA amplifications be handled? As you know, I favor the type of prospective sample collection you propose as a way of developing a prospective DNA registry. And perhaps we should decide a one format (blood sample, filter blood spot, or buccal smear) for this protocol. But, who will perform the amplification and at what estimated cost? The Duke CHG? Another Network center (remember we received 4 proposals last year)? Another company? I look forward to your response.
Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
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From:	Edward Donovan
To:	nfiner@pedsmail.ucsd.edu
Cc:	Cathy Grisby; Edward Donovan; Vivek Narendran; Higgins, Rosemary (NIH/NICHD) [E]; sduara@miami.edu; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
Subject:	SUPPORT
Date:	Wednesday, January 05, 2005 1:13:54 PM

Neil,
I can't believe I'm sending this email after all of our discussions.

For infants in the "surfactant group", to be extubated must they meet all of the extubation criteria? The protocol reads that extubation must be attempted within 24 hours of meeting all the extubation criteria. What I'm trying to figure out is under what criteria must they remain intubated?

Thanks,
Ed

Edward F. Donovan, M.D.
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From:	Neil Finer
To:	"Vivek Narendran"
Cc:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"
Subject:	RE: Support Trial
Date:	Tuesday, January 04, 2005 1:24:26 PM

Hi Vivek
All good questions
#1. If the team forgot the randomization card for any reason they should be instructed to treat the infant as if he/she were a CPAP infant. Intubate only for resuscitation indications, and if intubated then give surfactant and transfer to the NICU. As soon as possible, and it should be possible to get the actual randomization card within 30 minutes, open the envelope and if the infant is randomized to CPAP, carry on as initiated. If the infant is a Surfactant control, intubate and give surfactant within 1 hour of age. You would be following protocol for each of the arms.
#2 I would ask for IRB approval at Cincinnati Children's Hospital and move the infant with their oximeter, and continue the protocol. This will be the case in other centers as well.
#3 We use a combination of atropine 10-20 mics/kg, followed by either morphine (0.1mg/kg or fentanyl 2-3 mic/kg) and then mivacurium 200 mics/kg. We have found that the mivacurium wears off after 10 to 20 minutes, faster in the more mature infants, and is associated with good intubation conditions. We are seeing as we do another study, some more evidence of possible fentanyl related rigidity which makes me cautious about using fentanyl alone without a paralytic. In addition we believe that it is essential to maintain adequate lung volume before giving the narcotic and paralytic, and would advise that any necessary suction etc be done before they are administered, and that the infant receive adequate CPAP with good SpO2s until the actual intubation attempt. Failure to maintain such lung volume can be associated with significant desaturations.
I hope these comments are helpful.
Be well
Neil

-----Original Message-----
From: Vivek Narendran [mailto:Vivek.Narendran@cchmc.org]
Sent: Tuesday, January 04, 2005 7:01 AM
To: nfiner@ucsd.edu
Cc: Estelle Fischer
Subject: Support Trial

Dear Dr Finer,
Here are a few questions that were raised during our meeting yesterday in preparation to launch the support trial, that i need your input:
1)What if the resident/fellow/RT forgets to pick up the randomization card prior to reaching the delivery room? As we have two delivery hospitals, can we randomize all these infants into the treatment arm at University hospital (close to standard care) and control arm (close to standard care)at Good Sam Hospital, so that we don't loose patients who are already consented?
2)What happens to infants who are transferred out of the delivery hospital to Children's hospital within the first 14 days? Do we get IRB approval at Children's hospital to continue the trial (continue to manage them as per protocol, this is doable at Cincinnati) or they

automatically get out of the trial and we just follow their outcomes?
3)What's your suggestion on using combination drugs (sedation/analgesia/paralysis) for intubation? I guess we do whatever is the standard of care, but i am concerned about the kids in the treatment group who need to get intubated, as in my experience they invariably need higher pressures and support, once we take away their spontaneous efforts, despite the short half life of these drugs.
Vivek

Vivek Narendran MD, MRCP (UK)
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From: Higgins, Rosemary (NIH/NICHD)
To: indert@cryptic.rch.unimelb.edu.au
Subject: RE: NICHD NRN protocol review request
Date: Monday, January 03, 2005 8:41:00 AM
Attachments: Inder 1.3.05.doc
SC -SUPPORT.Hintz.secondary.rev.doc
Support protocol.pdf

Terrie
I have attached the neuroimaging secondary protocol to the main trial SUPPORT protocol. Please send your confidential review by January 30. If you have any questions, feel free to contact me. Thanks much in advance!

Rose

-----Original Message-----
From: indert@cryptic.rch.unimelb.edu.au [mailto:indert@cryptic.rch.unimelb.edu.au]
Sent: Saturday, January 01, 2005 7:08 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: NICHD NRN protocol review request

Dear Rosemary

I can review this grant by January 24th if it can be sent
via e-mail.

Many thanks

Terrie Inder

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of Child Health
and Human Development
Bethesda, Maryland 20892
6100 Executive Boulevard
Room 4B03
Rockville, MD 20852

DATE: January 3, 2005

TO: Dr. Terri Inder

FROM: Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPMRMC, NICHD, NIH

RE: Review of the protocol: Neuroimaging and neurodevelopmental outcome: A secondary to SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL (SUPPORT)

Enclosed you will find a copy of the protocol titled "Neuroimaging and neurodevelopmental outcome: A secondary to SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL (SUPPORT)" which the Neonatal Research Network's Steering Committee has approved. I have asked you, as one of a group of investigators with special expertise, to review the protocol for the Network. Please consider the following questions for comment in your review, which will be anonymous upon request.

1. Is the question significant? Is the question still unresolved?

2. What are the strengths and weaknesses of the following design elements:
   a. Primary and secondary outcome measures
   b. Eligibility, inclusion and exclusion criteria
   c. Study groups
   d. Assignment
   e. Masking
   f. Surveillance for complications
   g. Follow-up

3. Are there other important ancillary protocols (to be done at individual centers)? Should any ancillary project be a part of the primary study?

4. Do you anticipate any other problems with the trial?

Please feel free to comment on any other issues you feel are relevant.

Thank you for agreeing to review this protocol. The addition of external review to the process of protocol development of our trials has been invaluable.

Please email or fax your written response to me at higginsr@mail.nih.gov or (301) 496-3790 by January 30, 2005. Feel free to call me with any questions at (301) 435 - 7909

Susan Hintz, Stanford University

NEUROIMAGING AND NEURODEVELOPMENTAL OUTCOME: A SECONDARY TO SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL (SUPPORT)

A. Abstract/Statement of Problem

Cranial ultrasound (US) is currently used for brain imaging in the extremely preterm population, but this modality cannot detect subtle brain injury that may be responsible for later neuromotor and cognitive delay. Magnetic resonance imaging (MRI) can identify brain structural abnormalities and white matter injury better than cranial US. The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) will evaluate if permissive ventilation strategies and lower SpO_2 targets will result in increased rates of survival without bronchopulmonary dysplasia (BPD) and increased rates of survival without retinopathy of prematurity (ROP) among 24-27+6/7 week EGA infants. It is not known whether differing ventilation and oxygenation management approaches could lead to adverse consequences with respect to brain injury. Extremely premature infants are at very high risk for neuromotor and neurodevelopmental impairment, with reported rates of cerebral palsy (CP) ranging from 11-20%, and of severe cognitive delay ranging from 30-60%. Whether MRI and predict neurodevelopmental outcome better than early and/or late cranial US among preterm infants is not yet known, but small preliminary studies are promising. We therefore propose a secondary study to SUPPORT in which specifically timed cranial US (for SUPPORT subjects in all Network centers) and brain MRI (in Network centers able to participate in the brain MRI portion of this proposal) will be obtained. We will use neurodevelopmental follow-up data at 18-22 months corrected age to assess comparative and combined predictive capabilities of these neurodiagnostic modalities ("early" cranial US, "late" cranial US and MRI). We will also test the hypothesis that ventilation and oxygenation strategies in SUPPORT will not be associated with an increase in death or brain injury (Grade 3/4 IVH by cranial US at 7-14 days or 35-42 weeks, abnormal brain MRI at 35-42 weeks). The NICHD Neonatal Research Network is uniquely positioned to embark upon such a project, which would be the first multicenter, prospective study to investigate these important questions.

B. Objective

We propose a secondary, prospective study of cranial US at 7-14 days ("early") and 35-42 weeks postmenstrual age (PMA) ("late") (for SUPPORT subjects in all Network centers), and brain MRI at 35-42 weeks PMA (in centers able to participate in the brain MRI portion of this proposal) among infants enrolled in SUPPORT. We propose to evaluate and compare the capabilities of early and late cranial US and brain MRI to predict neuromotor and neurodevelopmental outcome at 18-22 months corrected age through development of predictive models.

We also propose to determine if ventilatory or oxygen saturation interventions are associated with differences in the outcomes of death or abnormal neuroimaging findings (death/grade 3/4 IVH on "early" US, death/grade 3/4 IVH on "late" US, death/PVL, death/abnormal MRI).

C. Hypotheses

- Multivariate modeling will demonstrate that conventional brain MRI at 35-42 weeks PMA will be superior to cranial US in predicting neurodevelopmental outcome at 18-22 months corrected age.
- There will be insufficient evidence to reject the null hypothesis that no differences exist in frequency of Death/Grade 3/4 IVH or Death/PVL on early or late US between Low and High SpO_2 groups, or between Early CPAP and Control ventilation groups
- There will be insufficient evidence to reject the null hypothesis that the frequency of Death/abnormal findings on conventional brain MRI at 35-42 weeks postmenstrual age (PMA) are not different between Low and High SpO2 groups, or between Early CPAP and Control ventilation groups.

D. Specific Aims

1) To obtain consistently performed, timed and interpreted neuroimaging studies in extremely preterm infants enrolled in SUPPORT:
    a. cranial US at 7-14 days of age (in all centers)
    b. cranial US at 35-42 weeks PMA (in all centers)
    c. MRI at 35-42 weeks PMA (in centers participating in MRI portion of this secondary)
2) To compare early and late US and MRI findings between Low and High SpO_2 groups, and between Early CPAP and Control ventilation groups.
3) To utilize the NICHD Neonatal Research Network follow-up programs to assess neurodevelopmental outcomes at 18-22 months corrected age, as described in SUPPORT.
4) To examine the independent associations of neuroimaging findings with neurodevelopmental outcomes through logistic regression modeling.
    a. Regression models will assess the absolute and relative value of early and late cranial US, and brain MRI, alone and in combination with traditional risk factors, to predict both abnormal and normal neurodevelopmental outcome at 18-22 months.
    b. Through stepwise regression modeling, we will also assess the value of neuroimaging findings, alone and in combination, in predicting neurodevelopmental outcomes over and above the value of early risk factors or early and in-hospital risk factors alone.

E. Background, Significance and Rationale

The importance of an advanced neuroimaging component to SUPPORT:

SUPPORT will be the largest randomized controlled trial of ventilatory and oxygen saturation target management in extremely premature infants to date. Although the primary outcomes for the SUPPORT focus on survival without BPD and survival without ROP, it will be crucial to evaluate the potential impact of study interventions on both neuroimaging findings and neurodevelopmental outcomes. One possible concern could be that lower oxygenation parameters and less aggressive ventilatory management may be associated with a higher incidence of brain injury. This position might be extrapolated from earlier observations in preterm infants (1,2), and from studies of near-term and term hypoxic brain injury.

Other investigations suggest that more aggressive ventilation strategies leading to hypocapnia may place the premature infant at higher risk for reduced cerebral blood flow (CBF) and subsequent white matter injury. The CBF-carbon dioxide reactivity observed in adult animals may be blunted or incomplete in newborn and preterm animals (3,4). Nevertheless, several clinical case series of preterm infants have demonstrated strong associations of hypocapnia with significant abnormal findings on brain imaging and with adverse neurodevelopmental outcome (5-8), although other important risk factors were also identified.

At the very least, neuroimaging abnormalities in preterm infants are likely to be the result of a multifactorial process. Emerging evidence points to the unique vulnerability of the preterm infant brain in several respects. Low blood flow to the cerebral white matter and impaired cerebrovascular autoregulation in premature infants (9-11) may make subtle brain ischemic injury more likely. Coupled with this tendency to ischemic injury, is the vulnerability of developing oligodendroglial cells to damage (see below). Finally, it is possible that effects of exposure to *in utero* infection, frequently suspected in extremely preterm infants, may potentiate brain cellular injury caused by mild to moderate ischemia (12,13).

Summary: Given the interventions to be undertaken in SUPPORT, and the complexity and multifactorial nature of the development of white matter injury in the premature brain, advanced neuroimaging could be a critical component to the trial. This proposed secondary to SUPPORT would provide important additional information to investigators with respect to the impact of respiratory management on subtle brain injury.

The need to investigate emerging brain imaging modalities:

Premature infants are at high risk for neuromotor and neurodevelopmental impairment. Recent reported rates of cerebral palsy (CP) at 18-24 months corrected age range from 11-20%, and of cognitive delay range from 30-60% for the extremely low birth weight (ELBW) population (14-16). Yet, despite numerous investigations, the complete explanation of these impairments remains unclear. Correlation of specific neonatal factors, particularly neuroimaging findings, with adverse neuromotor and neurodevelopmental outcomes are frequently demonstrated. Many studies have emphasized the association of cranial US abnormalities including intraventricular hemorrhage (IVH) grades 3 and 4, periventricular leukomalacia (PVL) and ventricular dilatation with subsequent neurologic and cognitive impairment (14-20). Most investigators have found abnormalities on cranial US to be an independent risk factor for neuromotor abnormalities, but not necessarily for cognitive impairment.

But, the finding of severe cranial US abnormalities is not uniformly predictive of adverse neuromotor outcome in the premature population. In a study of perinatal correlates of neurologic impairment at 18-22 months corrected age among VLBW infants (20), only 52% of the infants with CP on follow-up had had severe cranial US abnormalities. This finding was in contrast to a 12% rate of severe cranial US abnormalities among matched controls without CP. In a neurodevelopmental follow-up study of ELBW infants in a multicenter, double masked, randomized controlled trial of indomethacin prophylaxis in preterms (TIPP), rates of survival without neurosensory impairment were found to be similar between treatment groups although incidence of

grade 3 or 4 IVH on cranial US had been significantly reduced by treatment with indomethacin (21).

Smaller studies have investigated the capabilities of cranial US at term to predict CP among preterm infants, revealing that the sensitivity of this diagnostic tool is only approximately 60% (22,23). Other reports have indicated that cystic PVL may be detected in infants without previous cranial US abnormalities at several months of age (24-26). These studies suggest that only certain types of brain injury may be detectable with cranial US, and that timing of studies may be crucial. Furthermore, the radiologic changes associated with PVL may be visible by US only at a particular point in time; if cysts do not form as a result of injury leading to PVL, it may not be visible by US. Thus, injury could have occurred but would not be detected by US.

Summary: Cranial US, the imaging modality currently considered to be standard of care, may not be sensitive enough to detect brain injury that is responsible for later neuromotor or neurodevelopmental delay among ELBW infants.

MRI compared with cranial US to assess of brain injury and predict neurologic outcome

MRI provides a more complete and anatomically detailed evaluation of the neonatal brain. Several studies have compared the relative capabilities of US with MRI to detect brain injury among preterm infants in the newborn period. These reports concluded that MRI detects white matter injury better than HUS (27-29), and provides additional information regarding hemorrhage and cystic changes not noted by cranial US. Childs, et. al. assessed MRI and serial cranial US in both preterm and term infants, and concluded that MRI was more sensitive in identifying periventricular white matter lesions (30). However, neurodevelopmental outcome of the infants in those studies were not reported.

Few studies have compared MRI with cranial US in terms of their capabilities to predict neurodevelopmental outcome among premature infants; those are small, primarily single-center efforts. Furthermore, due to variability of timing, of imaging, and differences in MRI scoring and interpretation, the studies are difficult to compare. Valkama, et. al. (31) assessed MRI compared with cranial US performed at term in 51 VLBW, preterm infants (<34 weeks). Twelve infants were diagnosed with CP at 18 months corrected age. MRI parenchymal lesions predicted CP with 100% sensitivity and 79% specificity whereas US at term predicted CP with 67% sensitivity and 85% specificity. The authors concluded that MRI was the more reliable methodology. Stanford University researchers (see below "Preliminary Studies and Results") have completed a prospective study of neuroimaging among VLBW, preterm infants with neurodevelopmental follow-up at 18-22 months and 30 months corrected age (32). MRI at term predicted CP with superior sensitivity and positive predictive value compared with early cranial US.

Other studies have suggested the potential prognostic advantages of MRI compared with cranial US. Roelant-van Rijn and colleagues (33) studied 61 preterm infants with cranial US, and MRI within the first weeks of age and/or at term. MRI at term was found to be helpful in delineating internal capsule abnormalities, considered to be useful in predicting later hemiplegia. Other preliminary reports include that of Austin, et. al. (34) in which 93 VLBW infants evaluated with brain MRI at term underwent

neurodevelopmental assessments at one year corrected age. White matter injury on MRI at term was correlated with neuromotor abnormalities such as hypertonicity, hypotonicity, and motor delay. In a very small group of premature infants <36 weeks, Miller, et. al. (35) showed that cerebellar hemorrhages detected by MRI, even if not associated with white matter injury, appeared to be associated with adverse neurodevelopmental outcome at 12 months.

There are potential criticisms to these studies. In most cases, MRI was compared with only "late" cranial US or only "early" US; a more complete comparison would include both early and late cranial US, demonstrating that the design of neuroimaging collection strategies in prospective studies is crucial. Many studies focus narrowly on neuromotor outcome, specifically the prevalence of CP, as outcome variables. A broader neurodevelopmental assessment and comparison is warranted. Finally, all studies of MRI findings and correlation with neurodevelopmental outcomes in preterm infants thus far are small; it is therefore not possible to draw powerful conclusions, especially with regard to ELBW patients. In fact, the recently published "Practice Parameter: Neuroimaging of the Neonate" (36) failed to definitively recommend routine MRI for VLBW preterm infants in large part due to the lack of follow-up studies. But, many of the reports reviewed above were not available during the development of the "Practice Parameter".

Summary: Studies to date suggest that MRI may be a more powerful tool in predicting adverse neuromotor outcome among preterm infants. However, timing of studies vary between published reports, and very few prospective neurodevelopmental follow-up investigations have been undertaken to assess the comparative prognostic capabilities of these neuroimaging techniques for neuromotor and cognitive outcomes.

The importance of subtle white matter injury

Periventricular leukomalacia (PVL) has been categorized as "focal" and "diffuse" (37,38). Focal PVL has been described as the result of severe ischemic-necrotic injury and is located deep in the white matter. This type of injury may lead to the development of cystic changes or significant findings that can be detected by cranial US or conventional MRI. Diffuse PVL is thought to be the result of less severe injury, diffusely located in the white matter. The mechanism of diffuse PVL may be multifactorial, including: 1) mild to moderate ischemia due to decreases in cerebral blood flow consistent with impaired autoregulation, 2) vulnerability of immature oligodendroglial cells to ischemic injury and damage by chemical mediators, and 3) oligodendroglial cell susceptibility to injury and death after intraventricular hemorrhage due to creation of oxygen free radicals. The sensitivity of the immature oligodendroglial cells to cytokine-induced injury may help to provide a pathophysiologic explanation to the observations of increased CP rates among infants born to mothers with chorioamnionitis, and among infants with early sepsis.

Diffuse PVL may be a clinically important and prevalent white matter injury in the preterm infant. Yet, diffuse PVL is unlikely to be seen by cranial US. Diffuse PVL may also be challenging to detect reliably on conventional MRI. However, in a study by Counsell et. al. (39), diffuse excessive high signal intensity (DEHSI) in the white matter of preterm infants at near-term was associated with higher apparent diffusion coefficient

values on diffusion weighted MRI. This finding suggested that subtle injury, causing changes in cellular differentiation and probable preferential death of preoligodendrocytes, resulting in diffuse PVL (40), may be structurally visible in the form of DEHSI. The developmental significance for the preterm infant is not known. It is also important to note that not all subtle white matter injury is likely to be detectable even by MRI.

Summary: IVH and focal cystic PVL are detectable by conventional MRI or even cranial US. However, more subtle factors and injuries may lead to oligodendroglial cell death and diffuse PVL. Diffuse PVL is not likely to be detected by cranial US, but might be detected by MRI. Such injury may have a substantial impact on normal white matter development and neuromotor outcome in the preterm infant; however, this question has been poorly studied in a large-scale, prospective manner.

Preliminary Studies and Results

A coordinated effort among neonatologists, radiologists, engineers, technicians and developmentalists has been in place at Lucile Salter Packard Children's Hospital and the Lucas Center for Nuclear Magnetic Resonance at Stanford University since the late 1990's. The objective of this group has been to combine the talents and expertise from various fields of science to investigate novel, potentially clinically relevant neuroimaging approaches in term and preterm infants. As a result, a strong infrastructure exists to allow for the development and implementation of further prospective studies and trials of MRI in the neonatal population.

Cranial US vs. conventional MRI for prediction of CP in VLBW infants: Infants of <1250 grams and <30 weeks EGA were enrolled a prospective observational study of the capabilities of early cranial US compared with conventional MRI at near-term to predict CP at 18-22 months corrected age, and 30 months (32). Cranial US was obtained twice during the first two weeks of life, and the most abnormal findings were used for analysis. Conventional MRI and cranial US were scored with respect to size of hemorrhage, parenchymal involvement, and ventricular dilitation. 62 infants participated in the study, with one excluded from analysis due to a later diagnosis of muscular dystrophy. The sensitivity and specificity of near-term MRI for predicting CP at 18-22 months were 71% and 91% respectively. The sensitivity of MRI for predicting CP at 30 months of age increased to 86% with the specificity remaining high at 89%. Although the specificity was comparable to MRI, the sensitivity of US to predict CP was only 29% at 18-22 months and 43% at 30 months. The positive predictive value of US was 22% at 18-22 months and 33% at 30 months.

This study, one of the largest prospective comparative neuroimaging studies of VLBW infants and neurodevelopmental outcome, supports the suggestion that conventional MRI may be superior to cranial US with respect to prediction of neuromotor abnormalities. There are limitations to this study, however. Comparison cranial US were performed early in the hospital course (<2 weeks), and no US contemporaneous with the MRI were routinely obtained. Recent studies by other investigators have also determined that, among VLBW infants, early cranial US poorly predicts non-cystic white matter injury on MRI at term (41). Also, previous reports by

Valkama, et. al. (31) suggest that cranial US at term was a substantially less sensitive predictor of CP than MRI at term. Nevertheless, a thorough comparison would include early and later cranial US determinations to evaluate the potential combined prognostic power of early and late cranial US compared with MRI at term. In addition, this study was significantly limited by small sample size, with only seven infants diagnosed with CP on neurodevelopmental follow-up. Sample size considerations also restricted possibilities for multivariate modeling of outcomes, and meaningful analysis of Bayley Scales of Infant Development II scores. All of these limitations could be addressed in the proposed prospective multicenter study.

F. Research Design and Methods

1. Study Design: This proposed secondary to SUPPORT is a prospective study of traditional (cranial US at 7-14 days and 35-42 weeks PMA) and advanced (MRI at 35-42 weeks PMA) neuroimaging with respect to SUPPORT randomized ventilation and oxygen saturation interventions. The capabilities of these neuroimaging modalities to predict neurodevelopmental outcome at 18-22 months corrected age will also be assessed. **It is proposed that all subjects enrolled in SUPPORT should be able to participate in the cranial US portion of this proposal. It is understood that not all sites will be able to participate in the MRI portion of the proposed secondary. (SEE 3.b "Neuroimaging studies" below)**

Perinatal, demographic and neonatal data will be collected as part of the ongoing NICHD Neonatal Research Network Survey of Morbidity and Mortality Among VLBW Infants (401-1500g) for the purposes of the study. Cranial US will be obtained at 7-14 days and at 35-42 weeks PMA. *Clinical* interpretation of cranial US will continue to be performed at individual Network sites, but for purposes of research outcomes, cranial US should ideally be interpreted by central readers. Brain MRI will be obtained at 35-42 weeks PMA; MRI will be interpreted by a central reader(s) for purposes of research outcomes, but clinical interpretation will be performed at individual Network sites. Detailed neuromotor and neurodevelopmental examinations will be undertaken at 18-22 months corrected age as part of the NICHD Cooperative Multicenter Network of Neonatal Intensive Care Units: Follow-Up of ELBW Infants (401-1000g), and per SUPPORT protocol.

Statistical analysis will include bivariate analyses, and logistic regression modeling to 1) assess the association of SUPPORT ventilation and oxygenation randomized treatment groups with neuroimaging, 2) evaluate the strength of independent associations of specific neuroimaging findings with neurodevelopmental outcomes and 3) develop predictive models.

2. Study Population

Inclusion Criteria

- Enrolled in the NICHD Neonatal Research Network SUPPORT study
- **FOR ALL CENTERS:** Cranial ultrasound can be obtained at 7-14 days of age and at 35-42 weeks PMA
- **FOR CENTERS PARTICIPATING IN BRAIN MRI PORTION OF PROPOSED SECONDARY:** Brain MRI can be obtained per study specifications (see Appendix D) at 35-42 weeks PMA.

- If MRI cannot be performed by 42 weeks due to subject clinical condition (See Appendix B), the "late" cranial US would also be delayed such that the cranial US is within 7 days of the brain MRI.

Exclusion Criteria

- **FOR ALL CENTERS:** Patient is likely to be discharged or transferred by 35 weeks PMA to a facility where cranial US is NOT available.
- **FOR CENTERS PARTICIPATING IN BRAIN MRI PORTION OF PROPOSED SECONDARY:** Patient is likely to be discharged or transferred by 35 weeks PMA to a facility where cranial MRI is not available.
- Patient unlikely or family unwilling to participate in neurodevelopmental assessment at 18-22 month corrected age
- Presence of known or suspected congenital anomalies including:
  - ➤ Chromosomal anomalies
  - ➤ Complex congenital heart disease (PDA, small muscular VSD or PFO are NOT considered to be congenital heart disease for the purposes of this study)
  - ➤ Congenital infection (TORCH, untreated maternal HIV, syphilis)
- Lack of informed consent

Enrollment of Subjects

Screening: Each center will be responsible for devising a screening strategy to identify all potential participants using the study inclusion and exclusion criteria. Screening and identification of patients should take place by 14 days of age since the "early cranial US" must be performed at 7-14 days.

Informed consent: Each participating center will follow procedures for developing informed consents as set out by the local Institutional Review Board (IRB). It is expected that the parents of all eligible infants will be approached to participate in this prospective study, and informed consent must be obtained by the individual center.

Eligible infants not enrolled: The reasons for non-enrollment will be documented. Short- and long-term outcomes of eligible infants not enrolled in this study will be documented as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality in VLBW Infants (Generic Data Base (GDB)) and, if enrolled, as part of the ongoing NICHD Neonatal Research Network ELBW neurodevelopmental follow-up study.

No MRI obtained for infants enrolled in the MRI portion of the study: An important objective of the proposed study requires acquisition of MRI at 35-42 weeks PMA; it is important that each participating center make this a priority. However, it is understood that if the patient is deemed medically unstable (Appendix B) during the entire 35-42 week PMA period, an MRI will not be obtained during that period. If the patient is medical unstable, MRI MAY BE DELAYED beyond 42 weeks, however LATE CRANIAL US SHOULD ALSO BE DELAYED in that case, such that the studies are still obtained within 7 days of each other.

3. BASELINE DATA, NEUROIMAGING, NEURODEVELOPMENTAL FOLLOW-UP

a. Baseline Data: Perinatal, demographic and in-hospital variables

i. INTRODUCTION AND FEASIBILITY: This secondary protocol will not require substantial data collection in addition to that already in place at participating centers; nor

will it mandate patient management. The majority of data collection instruments will be those already in routine use in the participating centers through the NICHD Neonatal Research Network Survey of Morbidity and Mortality in VLBW Infants. These data are obtained through the use of "Generic Data Base forms" which allows for consistent accrual of demographic, perinatal and neonatal variables among this high-risk population.

ii. METHODS: Research nurses at participating centers will collect data using the standardized Generic Data Base Forms. Additional queries will attempt to delineate the potential independent contribution of hypotension and hypocarbia, purported to be causes of cerebral hypoperfusion (42-46) leading to diffuse or focal neonatal brain injury, to abnormalities on MRI. These questions will be coordinated with the SUPPORT protocol subcommittee and focus on 1) need for pressors and 2) the degree of hypocarbia experienced

Since these infants will be participating in the SUPPORT trial, information regarding ventilation strategy and oxygen saturation randomization arms will also be available.

b) Neuroimaging studies

i. INTRODUCTION AND FEASIBILITY: Changes in the approach to neuroimaging may be required for implementation of this research protocol at participating centers. The extent of the changes will depend upon the procedures already in place at each individual center, and the level of participation (i.e., cranial US portion ONLY vs. cranial US and brain MRI portions of this secondary). In addition, budgetary constraints may limit participation.

CRANIAL US: Within the Neonatal Research Network, cranial US should already routinely be performed in ELBW infants 7-14 days of age window, and should also be performed at near-term among sites that are not performing MRI as the near-term brain imaging modality. The most recent results (November 2004) of the Preterm Infant Neuroimaging Questionnaire indicate that all but one Network center reported that cranial US are routinely obtained at 7-14 days among infants <28 weeks EGA. The one remaining center reported obtaining cranial US earlier than 7 days. Therefore, for the cranial US portion of this proposed secondary, **no additional imaging would be required for sites using only US as the routine neuroimaging modality.** For the purposes of this study however, central neuroimaging readers should ideally be used for both early and late cranial US since disparate interpretations of would potentially complicate analysis. Additional costs would therefore be incurred with respect to coordinator time (tracking, gathering, sending studies) and central reading.

BRAIN MRI: The most recent results (November 2004) of the Preterm Infant Neuroimaging Questionnaire reveal that two Network sites currently use brain MRI as the routine near-term VLBW imaging modality, with one additional site planning to implement routine MRI, and 4 other sites "considering" a change to MRI. Therefore, for those sites utilizing MRI as the routine near-term neuroimaging modality, **only one additional study, a cranial US at near-term, would be required.** In addition to the cost of the additional imaging study, costs would be incurred as noted above with respect to coordinator time and central reading.

WHICH CENTERS WILL PARTICIPATE IN THE BRAIN MRI PORTION OF THIS PROPOSED SECONDARY? Network centers with devices capable of performing neonatal conventional brain MRI (4 mm slice) could participate in the MRI portion of this proposed study. **Sites not performing brain MRI as the routine near-term neuroimaging study MAY be able to participate in the Brain MRI portion of this secondary. However, due to budgetary considerations, it is possible that implementation of this proposed secondary may be limited only to selected Network sites.** The most conservative approach would be that only those sites in which MRI is currently, or will soon be, implementing routine near-term MRI will participate in this proposed secondary.

ii. METHODS:

1) "Early cranial ultrasound": A cranial ultrasound will be obtained at 7-14 days of age. If more than one cranial ultrasound is obtained during that time period, the ultrasound obtained closest to 14 days will be used. Results will be interpreted as indicated in the Manual of Operations (See Appendix C), and reported in the NG03 form, but central readers will formally interpret ultrasounds.

Although not currently *required* within the parameters of the NICHD Neonatal Network VLBW Registry, recent ELBW neurodevelopmental follow-up studies from the NICHD Neonatal Research Network reveal that virtually all of these extremely high risk infants surviving to the 18-22 month visit have had at least one cranial US early in the course of their hospitalization. Furthermore, the "Practice Parameter" for neuroimaging in the neonate recommends *screening cranial US should be performed on all infants with EGA of <30 weeks at 7-14 days of age* (36); it is likely that Network centers have already implemented this practice to patient care protocols.

2) "Late cranial ultrasound": A cranial ultrasound will be obtained at 35-42 weeks PMA, and within 7 days of brain MRI. All late cranial US will be reported in the NG03 form as indicated in the Manual of Operations (See Appendix C), and will be interpreted by central readers.

Late cranial US is not currently required in the Network paradigm. However, the "Practice Parameter" as referred to above (36) recommends that *cranial US should be optimally repeated at 36-40 weeks' postmenstrual age*, so it is likely that Network sites have implemented this routine imaging.

FOR CENTERS PARTICIPATING IN THE BRAIN MRI PORTION OF THE PROPOSED STUDY:

3) Brain MRI: A brain MRI will be obtained at 35-42 weeks PMA, and within 7 days of the "late cranial ultrasound". Images will be acquired as described in Appendix A. Conventional MRI images will be transferred to Stanford University for interpretation and scoring by central pediatric neuroradiologist reader(s) (Patrick Barnes, M.D., and others as suggested by the Steering Committee) who will be masked to any unique patient identifiers and to patient history and outcome. Dr. Barnes is a highly regarded, widely published pediatric neuroradiologist with extensive experience in the field of MRI, MR spectroscopy, diffusion weighted and diffusion tensor imaging. In addition to his dedicated work at Stanford University, Dr. Barnes has also collaborated with researchers such as TE Inder, PS Huppi and JJ Volpe. Dr. Barnes is an expert in the timing of fetal and neonatal brain injury using methods such as MRI and MRS.

MRI interpretation and data access: Conventional MRI images will be interpreted and scored by a central neuroradiology reader (Appendix C). The central reader(s) will be responsible for completion of data forms and data transfer to the Network Data Center. Each participating center is expected to counsel families with regard to MRI findings on the basis of its own neuroradiologist's interpretation of the images.

Sedation issues: MRI studies are performed without sedation at Stanford University. Patients are imaged following a feeding, ear plugs (MiniMuffs, Natus) are used to reduce the noise by up to 50% and patients are bundled to preserve warmth, maintain sleep and reduce patient motion. Of the 14 sites that responded to an earlier NICHD Neonatal Research Network Brain Imaging Survey (Dr. Seetha Shankaran), five indicated that they already use sedation for MRI. Another six sites indicated that sedation is used if clinically necessary. One site responded that sedation is not used. Responses from two centers were not clear. At Stanford, the approach of "feeding and swaddling" has yielded successful conventional MRI imaging with excellent quality in almost all cases. Sedation, if needed, would clearly increase the likelihood of obtaining a high quality scan. Network centers in which sedation is standard of care, and MRI is routinely performed, should certainly be able to continue their current approach. Although several of the sites have already indicated that sedation is used routinely, it is appreciated that the use of sedation in the context of a research protocol may make IRB approval more difficult. One possible solution for centers with such challenges would be to present two consent forms: the first for participation in the study itself, indicating that "feeding and swaddling" methods would be tried; the second, for consent to use sedation if this conservative approach were not successful, or if it is considered medically inadvisable to implement the "feeding and swaddling" approach (i.e., severe reflux). Clearly there are differing approaches to sedation for MRI studies, thus the issue of sedation will be left to the individual investigators at each Network site.

c) Neurodevelopmental Follow-up

i. INTRODUCTION AND FEASIBILITY: Neurodevelopmental follow-up for ELBW infants is already a focused objective within the NICHD Neonatal Research Network; all Network centers have complete neurodevelopmental assessment teams and patient tracking infrastructure in place. In addition, neurodevelopmental follow-up is already a part of SUPPORT protocol.

ii. METHODS: Follow-up visit will be conducted at 18-22 months corrected age as described in the "NICHD Neonatal Research Network ELBW Follow-Up Study Manual of Operations" (see Appendix C). An exam for neurological exam for cerebral palsy will be performed. The Bayley Scales of Infant Development (Bayley N. Bayley Scales of Infant Development-II. San Antonio, TX: Psychological Corporation; 1993) will be administered by a Bayley Examiner certified for the Follow-Up Study. In addition to neurodevelopmental assessments, information regarding socioeconomic status, level of education of the primary caregiver, and marital status is routinely obtained at the 18-22 month visit.

4. STATISTICAL CONSIDERATIONS

Outcomes:

Primary outcomes considered will include

- Death/Grade 3/4 IVH on 7-14 day cranial US
- Death/Grade 3/4 IVH on 35-42 week cranial US
- Death/PVL on 35-42 week cranial US
- Death/abnormal MRI at 35-42 weeks

Secondary outcomes will include
- cerebral palsy
- BSID MDI<70
- BSID PDI<70
- Neurodevelopmental impairment (NDI) defined as any of the following: deafness, blindness, moderate-severe cerebral palsy, or BSID II MDI or PDI score <70.

Bivariate analyses: Analyses of frequency of primary outcomes with respect to SUPPORT treatment groups will be undertaken. Comparisons will be made between ventilation strategy groups (Early CPAP and Control groups) within each randomized oxygenation group, and between oxygenation strategy groups (Low and High SpO2) within each randomized ventilation group. Continuous measures will be compared using the Student t-test and ANOVA where appropriate, and Chi-square analysis will be used to compare categorical data. These analyses would also adjust for the clustering effect introduced by randomizing by week of study.

Sample size and power issues:
Overall GDB and follow-up patient numbers: For year 2003, 1468 infants 24+0 to 27+6 weeks EGA were enrolled in GDB. Of those, 1249 survived to >7 days and 1209 survived to >=14 days. 1027 patients survived to hospital discharge. In year 2003, a total of 725 former 24+0 to 27+6 week EGA patients completed neurodevelopmental assessment at 18-22 months corrected age.
Frequency of neuroimaging outcomes:
Ultrasound: For year 2003, among infants 24+0 to 27+6 weeks EGA surviving to >=14 days, the frequency of Grade 3/4 IVH on cranial US was 20.3%; for those surviving to discharge it was 18.6%. The frequency of PVL among those surviving to discharge was 3.9%.
MRI: "Abnormal" conventional MRI results among preterm infants at near term are much more difficult to quantify. This is due both to a paucity of available data in the literature, and disparate methods of reporting and scoring "abnormalities" on brain MRI among preterm infants. Two recent studies have attempted to estimate the frequency of white matter signal abnormality, as well as other abnormal findings. Inder and colleagues (47) reported on findings of brain MRI performed at term equivalent age in 100 infants of 23-32 weeks EGA. Only 36/100 were considered to have no white matter signal abnormality, whereas 16/100 had extensive severe white matter signal abnormality. Cortical gray matter abnormalities were rare, with 96/100 patients categorized as normal. Lateral ventricle size was normal in only 40/100. Miller, et. al. (48) reported on MRI findings of 32 consecutive preterm infants, but imaging was performed at earlier postconceptual ages. In addition, previous studies by Maalouf (27) found that 12/19 (63%) preterm infants studied by MRI at 38-44 weeks PCA had abnormal white matter signal, but of those only 7 were moderately to severely abnormal (37%). Childs (30)

found 29 of 105 preterm infants (<37 weeks) had abnormal periventricular white matter on MRI, and an additional 5 infants with other abnormalities (32% abnormal). However, the age at the time of MRI in that study ranged from 1-42 days, and PCA at time of scan was not reported. Counsell, et. al. found that, among preterm infants at near term, 34 of 50 had "overt" white matter abnormality or diffuse excessive high signal intensity white matter abnormalities (68% abnormal) (39). In summary then, the frequency of "abnormal" brain MRI in preterm infants ranges from 32-68%. One projected benefit from this proposed secondary study, in fact, would be that the frequency of specific MRI abnormalities in a large premature group could be better clarified and described. For the purposes of sample size and power calculations for this proposal, a conservative estimate of 40% white matter abnormality by MRI at 35-42 weeks will be used.

Thus, the following are the estimated rates for four major outcomes examined in this proposal:

I) Death/Grade 3/4 IVH (14 day)	34.2%
II) Death/Grade 3/4 IVH (at d/c, an estimate of 35-42 weeks)	42.9%
III) Death/PVL (at d/c, an estimate of 35-42 weeks)	32.8%
IV) Death/MRI abnormality	58%

Sample size and detectable difference estimates if all centers could participate in both cranial US and brain MRI portions of study:
The revised projected sample size required for SUPPORT is 1310 patients (or 328 patients per each of 4 treatment groups). It is unlikely that all centers could participate in both cranial US and Brain MRI portions of this proposed study. But, if one used an estimate of 80% enrollment in the proposed study, 1048 patients would be enrolled. This would provide 262 patients in each for 4 groups, such that bivariate comparisons will be made between ventilation strategy groups (Early CPAP vs. Control ventilation groups) within each randomized oxygenation strategy, and between oxygenation strategy groups (Low vs. High SpO2) within each randomized ventilation strategy.

Note that 80% enrollment should be considered a conservative estimate for the cranial US portion of this study – virtually all SUPPORT subjects should be able to participate in the cranial US portion of this study.

Thus, for the outcome of Death/Grade 3/4 IVH (14 day), using an expected prevalence rate of 34.2% (see above), a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	33.9% = 34.2% to 22.6%
% increase from expected	35.9% = 34.2% to 46.4%

For the outcome of Death/Grade 3/4 IVH (35-42 week), using an expected prevalence rate of 42.9%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	28.4% = 42.9% to 30.7%

% increase from expected 29.4% = 42.9% to 55.4%

For the outcome of Death/PVL by cranial US (35-42 week), using an expected prevalence rate of 32.8%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected 34.4% = 32.8% to 21.5%
% increase from expected 36.9% = 32.8% to 44.9%

As noted above, it is unlikely that 80% enrollment could be achieved for the Brain MRI portion of this study. However, if this were to be possible, the following would apply:

For the outcome of Death/MRI abnormality (35-42 week), using an expected prevalence rate of 58%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected 21.6% = 58% to 45.5%
% increase from expected 20.7% = 58% to 70%

The detectable differences were also calculated for an alpha of 0.01 to adjust for the four primary outcomes. Thus,

For the outcome of Death/Grade 3/4 IVH (14 day), using an expected prevalence rate of 34.2% (see above), a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected 40% = 34.2% to 20.5%
% increase from expected 43.2% = 34.2% to 49%

For the outcome of Death/Grade 3/4 IVH (35-42 week), using an expected prevalence rate of 42.9%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected 33.6% = 42.9% to 28.5%
% increase from expected 35.2% = 42.9% to 58%

For the outcome of Death/PVL by cranial US (35-42 week), using an expected prevalence rate of 32.8%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected 40.2% = 32.8% to 19.6%
% increase from expected 42.7% = 32.8% to 46.8%

For the outcome of Death/MRI abnormality (35-42 week), using an expected prevalence rate of 58%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	25.8% = 58% to 43%
% increase from expected	24.8% = 58% to 72.4%

If MRI could not be performed in all sites due to budgetary constraints, clearly differences between groups with respect to the outcome of Death/MRI abnormality would need to be larger in order to detect. If the number of patients involved in the MRI portion of the proposed study were reduced by one-half (to 524), then the sample size per group would drop to 131. In that case:

For the outcome of Death/MRI abnormality (35-42 weeks), using an expected prevalence rate of 58%, a projected sample size of 131 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	37% = 58% to 36.5%
% increase from expected	35.5% = 58% to 78.6%

However, recall that the estimate of 40% white matter abnormality on MRI among preterm infants at term is conservative, thus the estimate of 58% for the outcome of Death/MRI abnormality may also be conservative.

Regression Analyses: In addition to bivariate analyses, regression analyses will be undertaken to attempt to adjust for confounding variables in comparisons of treatment groups with respect to neuroimaging findings. The independent association of ventilation strategy will be determined for each neuroimaging outcome (Grade 3/4 IVH at 7-14 days, 35-42 weeks, PVL at 35-42 weeks, MRI abnormality), adjusting for gestational age, weight, and oxygenation strategy. Similarly, the independent association of oxygenation strategy will be determined for each neuroimaging outcome (Grade 3/4 IVH at 7-14 days, 35-42 weeks, PVL at 35-42 weeks, MRI abnormality), adjusting for gestational age, weight, and ventilation strategy.
Neurodevelopmental Outcomes Logistic Regression Models: We propose a novel approach to the comparison of neuroimaging modalities with respect to neurodevelopmental outcomes, that of logistic regression modeling. Numerous neurodevelopmental outcomes studies have used this approach, however previous studies of brain MRI in the premature infant have lacked the sample size to implement this statistical technique. Models will be developed to include perinatal, demographic, neonatal and socioeconomic factors pertinent to neurodevelopmental outcome as demonstrated in previous reports (14,15) and the univariate and multivariate analyses carried out. Neuroimaging study results (cranial US at 7-14 days, cranial US at 35-42 weeks PMA, and brain MRI at 35-42 weeks) will be added to the model individually and in combination, to determine the adjusted risk for adverse outcome that each imparts, and to ascertain if any two abnormal studies (i.e., early cranial US and MRI, or early and late US) are materially more predictive of neurodevelopmental impairment than any single abnormal study. Ventilatory strategy and oxygen saturation strategy will also be available as crucial neonatal factors that may impact on outcome.

Predictive modeling of outcome: Challenges to the development of a predictive model include the need for both a "model development" data set and a "model validation" data set. Possible solutions to this challenge include splitting the proposed study data set in half, thus creating a development and validation set; or by employing a so-called "boot-strapping" technique by which multiple random samples of the data set are used for calculating confidence intervals for predictions (49). Further analysis will be required to determine the best strategy for predictive modeling in the proposed study.

Further Statistical considerations: Development and comparison of predictive models:

I. Initial model development, the models and their variables.

The sample will be randomly split into a development dataset with 50% of cases and 50% of controls and a test dataset with 50% of cases and 50% of controls. Several models will be developed of which the following are projected to be central models; however, additional models may also be developed:

1. "Classic" risk model, including traditional factors (i.e., gestational age, birth weight, gender, race, maternal education, etc.) as well as "worst" early cranial US
2. Late cranial US model
3. Conventional MRI model

For each model, the number of categorical variables will be restricted to 5 – 10 observations per category cell. When candidate variables exceed this ratio, the best set of significant predictor variables will be chosen by forward selection. In this case, at each step the variable with the most significant effect will be identified and added to the model. The same dataset will be used for the development of each model.

II. Model calibration and goodness-of-fit

Each model will be calibrated using Pearson chi-square, likelihood ratio chi-square, and Hosmer and Lemeshow statistic.

III. Model discrimination and predictive ability

Sensitivity (true positive rate) and specificity (true negative rate) of the models to predict outcome will be evaluated. The receiver-operator curve (ROC) will be used to display model discrimination by plotting sensitivity against specificity. The predictive abilities of the models will be compared using area under the curve (AUC) analyses (Hanley JA and McNeil BJ, *Radiology* 1982)

IV. Multidimensional model.

Finally, we will attempt to build a model that combines the most significant factors from cranial US and MRI models and compare to the above models.

APPENDICES

Appendix A: Magnetic resonance imaging requirements and image acquisition

Conventional MRI: Network centers that have any "type" of device (i.e., GE, Philips, Siemens, etc.) capable of performing standardized conventional neonatal brain MRI

sequences with 4 mm contiguous slices (0mm gap) will be able to participate. All examinations will include conventional fast spin echo (FSE) T1-weighted and T2-weighted sequences as well as fluid attenuated inversion recovery (FLAIR) and gradient echo (GRE) sequences.

Appendix B: Medical instability at 35-42 week PMA MRI

For "medical instability" to be considered the cause of non-acquisition of MRI, one of the following conditions should exist during the entire 35-42 week PMA MRI imaging window:

- The patient is intubated.
- The patient is considered by the attending neonatologist to be critically unstable such that transport to the radiology suite would be unsafe.

Appendix C: Neuroimaging and neuromotor evaluation

Ultrasound scoring instruments will be modified from the PiNO central reader forms, but will include reference to the following findings, and will be delineated as unilateral or bilateral:

Early Cranial Ultrasound:

- Grade I: blood/echodensity in the germinal matrix/subependymal area
- Grade II: blood/echodensity in the lateral ventricle without distention
- Grade III: blood/echodensity in the lateral ventricle with distention
- Grade IV: blood/echodensity in the parenchyma
- Periventricular leukomalacia
- Cystic periventricular leukomalacia

Late Cranial Ultrasound

- See above
- Porencephalic cystic changes
- Ventriculomegaly
- Presence of shunt

Adjustments and amendments to the following MRI interpretation scheme may be made after further discussion and input from members of the Steering Committee and SUPPORT Subcommittee.

Conventional MRI interpretation:

- C1 = normal
- C2 = minimal subependymal hemorrhage or mineralization with no or mild ventriculomegaly
- C3 = moderate to severe ventriculomegaly
- C4 = parenchymal abnormality
- C5 = periventricular cystic abnormality
- C6 = white matter signal abnormality
- C7 = increased extra-axial fluid
- C8 = cerebellar hemorrhage or mineralization
- C9 = diffuse excessive high intensity signal

Cerebral Palsy ("Neonatal Research Network Follow-Up Study Manual of Operations")
Cerebral palsy at 18-22 months will be diagnosed if definite findings are encountered on exam in any two of the following three areas:

1) Delay in motor milestones – determined using the motor quotient as described in the Manual of Operations.
2) Abnormalities observed in the classical neuromotor exam, which includes measurement of tone, deep tendon reflexes, coordination and movement (not including eye movement). Any one abnormality, except for isolated low tone or toe walking is sufficient.
3) Aberrations in primitive reflexes and postural reactions – any aberration is sufficient.

Cerebral palsy will be further categorized by type and severity, as described in the Manual of Operations.

Human Subjects

1. Risks to the subjects:

a) Human Subjects Involvement and Characteristics: Infants enrolled in the NICHD Neonatal Research Network SUPPORT trial will be recruited. Inclusion and Exclusion criteria have been defined as stated in the Research Plan. The final population will be dependent upon the number of sites within the Network that participate in this study. Both male and female infants will be enrolled. We expect the study population to be representative of the racial background and gender distribution of the Neonatal Research Network. In 2001, 49% male and 51% female patients constituted the ELBW population of the Neonatal Research Network, of which 43% were black, 38% were white, 15% were hispanic, and 3% were other races.

b) Sources of Materials: Sources of research material will consist of perinatal, demographic and neonatal data collected by research personnel as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality Among VLBW Infants (401-1500 g), and through the data collection mechanisms associated with the SUPPORT trial. Additional data will be obtained through evaluation of brain MRI images by a central reader masked to all patient identifiers and patient outcomes. Data forms will be created, completed by the central MRI reader, and submitted to Research Triangle Institute per protocol. Neurodevelopmental outcome data will be obtained from the NICHD Neonatal Research Network Follow-up Study of ELBW Infants, and per SUPPORT specifications.

c) Potential Risks: The risks and discomforts of participation are minimal as the study relies primarily on data collected for ongoing studies already in progress, and uses non-invasive techniques. Cranial US is performed routinely in all NICU's in the NICHD Neonatal Research Network, is considered standard of care, and techniques would not be altered by this study. Brain MRI at 35-42 weeks postmenstrual age is already routine in several Network centers. Sedation will not be used routinely, although may be used particularly in centers that already do use sedation. Temporary minor skin irritation from tape used to apply MRI-compatible monitoring electrodes may occur, but this risk is unlikely. Temporary transport of a patient to a radiology suite for MRI may also represent a possible risk; however, only those patients considered stable for transport will undergo imaging, and a 7- week window of opportunity for MRI is built into

the proposed study. The alternative to obtaining a brain MRI as part of the proposed study is non-enrollment.

2. Adequacy of Protection Against Risks:
a) Recruitment and Informed Consent :
Screening: The individual center will be responsible for devising a screening strategy to identify all potential participants using the study inclusion and exclusion criteria. Screening, identification and informed consent procedures should be completed by 14 days of age as "early cranial US" must be performed by this time.
Informed consent: Each participating center will follow procedures for developing informed consents as set out by their Institutional Review Board (IRB). The parents of all infants enrolled in SUPPORT will be approached to participate in this secondary study, and informed consent must be obtained by the individual center. Informed consent will be obtained by the Principal Investigator or his/her designee.
Eligible infants not enrolled: The reasons for non-enrollment of eligible infants will be documented. Short- and long-term outcomes of eligible infants not enrolled in this study will be documented as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality in Very Low Birth Weight (VLBW) Infants (Generic Data Base (GDB)) and, if enrolled, as part of the ongoing NICHD Neonatal Research Network ELBW Neurodevelopmental Follow-Up Study.
No MRI obtained for enrolled infants: The objective of the proposed study requires acquisition of cranial US and MRI at 35-42 weeks PMA; if the patient is deemed medically unstable during the entire 35-42 week PMA period, an MRI will not be obtained. Other reasons for inability to obtain the MRI will also be documented.
b) Protection against risk: Every effort will be made to protect study patients from potential risks of participation. Stability of study patients for transport to a radiology suite for brain MRI will be assessed by the attending neonatologist at each participating site. Should a patient be judged to be unstable for transport to the radiology suite, a 7-week window of opportunity for MRI (35-42 weeks postmenstrual age) has been provided in the protocol. Any adverse events with regard to obtaining neuroimaging studies among enrolled patients will be documented and submitted to NICHD, the data center, and the local IRB. The NICHD Neonatal Research Network has an independent Data Safety Monitoring Committee (DSMC), which would provide continuous oversight of patient safety and risk factors for the duration of the study. The DSMC will review the study on at least an annual basis.

3. Potential Benefits of the proposed research to the subjects and others: The potential benefits of participation to an individual patient include identification of structural anomalies by MRI that would not have been identifiable by ultrasound. This may allow for early, targeted intervention for the individual patient that otherwise would not have been undertaken. Other potential benefits would be to future extremely preterm patients after results of this prospective study are known (see below).

4. Importance of the knowledge to be gained:
Provide a thorough neuroimaging monitoring arm for SUPPORT: Although cranial US is a standard diagnostic procedure in the NRN, the proposed study would provide a

framework for specifically timed cranial US studies, which would be more appropriately comparable. In addition, subtle but arguably extremely important findings consistent with brain injury would be detectable by MRI.
Counseling, follow-up: Detection of an injury pattern which is consistent with later neurodevelopmental delay will be useful for counseling and targeted, early follow-up. Identifying such a tool would provide a link to later research in early intervention.
Clarify the pathogenesis of injury leading to neurodevelopmental impairment: Further delineation of pathophysiologic correlates of later outcome could possibly be linked with perinatal and neonatal factors, which would 1) focus future research and intervention on clinical events associated with the pathophysiologic hallmark, 2) provide important data leading to further study of the pathogenesis and timing of injury, and 3) assess neuroanatomic localization of subtle injury associated with later neuromotor abnormalities.
Contribution to the literature with respect to diagnostic strategies for the extremely preterm population: Previous neuroimaging practice parameters have concluded that insufficient evidence exists to recommend advanced neuroimaging for premature infants for prediction of neurodevelopmental outcomes. The proposed study would address this significant gap in the collective literature.

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Protocol for the NICHD Neonatal Research Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial

Final

August 28, 2004
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1.1 Statement of Problem

At the present time, there is no recommendation or standard teaching regarding the early use of CPAP/PEEP during resuscitation and continuing after NICU admission for the extremely low birth weight (ELBW) infant. However, a number of studies, mostly retrospective in nature, have suggested that the use of early CPAP may be associated with improved outcomes, including a decreased need for mechanical ventilation, a decreased need for surfactant therapy, and a decrease in oxygen supplementation and/or death at 28 days after birth and at 36 weeks post menstrual age. There has not been a prospective study which has randomized ELBW infants to CPAP/PEEP beginning in the delivery room, and continuing in the NICU and a permissive ventilation strategy if intubation is required and compared their outcomes to infants treated with prophylactic or early natural surfactant, interventions with known efficacy in reducing mortality, severity of disease and the incidence of chronic lung disease (CLD).

Retinopathy of prematurity (ROP) remains a significant cause of morbidity among ELBW infants and its occurrence is inversely proportional to gestational age and duration of oxygen exposure. It is known that ROP is increased by the prolonged use of supplemental oxygen from observations published in the 1950s, and but early trials were unable to pinpoint the actual level of arterial PaO_2 which was the threshold for triggering the pathophysiology of this disorder.[1] However, there have been a very few prospective studies evaluating the benefit of higher versus lower levels of oxygenation in infants, especially for ELBW infants, none of which were performed during the acute illness. While retrospective cohort studies have suggested that the use of lower SpO2 ranges and adherence to strict nursery policies may result in a lower incidence of severe ROP, there is no current agreement on the accepted SpO2 ranges for managing the ELBW infant from birth.

1.2 Background

Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC). Although no formal recommendation has been made to date about maintaining PEEP in the delivery room setting, continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[2]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9hours ($\pm$12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[3] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[4]. Premature infants who do not achieve a FRC are more likely to develop hyaline membrane disease (HMD) requiring mechanical ventilation[5]. CPAP may prevent the excessive consumption of surfactant in newborn infants with limited surfactant production.[6] A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era suggested that early CPAP may improve survival in infants greater than 1500 gm.[7]

Similarly, there is no definite recommendation or standard teaching regarding the level of oxygenation that should be maintained in ELBW infants. Oxygen supplementation has to be used liberally as ELBW infants frequently have desaturation episodes and thus wide saturation ranges are tolerated clinically. However, oxygen toxicity can result in increased risk for CLD, retinopathy of prematurity (ROP) and other disorders. Alternatively, oxygen restriction may impair neurodevelopment. The pulse oximeter is a newer technology that can be used to improve the control of oxygenation levels. There is great potential benefit to determining the oxygenation levels that prevents ROP and CLD but does not result in neurodevelopmental impairment with a randomized controlled trial of levels of oxygen saturations on the high and low side of the currently utilized levels.

While prevention of hyperoxia may decrease the risk for ROP and CLD, efforts to maintain lower oxygenation levels may result in an increase in periods of hypoxemia because of the marked variability in oxygen in ELBW infants. Thus, it is necessary to determine if lower oxygenation levels that may prevent ROP and CLD are deleterious for brain development and result in impaired neurologic outcome.

1.3 Animal Studies

Nilsson et al demonstrated that the use of 5 cm H_2O PEEP in the initial ventilation of premature rabbit pups resulted in increased lung-thorax compliance, and reduced the extent of bronchiolar epithelial lesions seen with mechanical ventilation [8]. The use of early PEEP starting at delivery, improves the response to surfactant, improves lung mechanics increases surfactant pools, and reduces lung injury. [9,10]

More recently studies by Jobe et al have demonstrated that premature lambs treated with CPAP alone at birth had significantly decreased neutrophils and hydrogen peroxide in their alveolar wash when compared with animals who were ventilated from birth.[11]

1.4 Human Experience: Ventilatory Support

CPAP was introduced by Gregory et al in 1970 and was shown to improve gas exchange and outcomes in preterm infants with respiratory distress.[12] A subsequent review of CPAP for respiratory distress concluded that "In preterm infants with RDS the application of CDP either as CPAP or CNP is associated with benefits in terms of reduced respiratory failure and reduced mortality. CDP is associated with an increased rate of pneumothorax. The applicability of these results to current practice is difficult to assess, given the intensive care setting of the 1970s when four out of five of these trials were done."[13]

There is now a body of information from Europe that provides further evidence that early CPAP can reduce the need for intubation in a significant number of VLBW infants. Jonsson et al treated VLBW infants from 1988 to 1993 that required > 30% oxygen with nasal CPAP usually within 30 minutes of delivery[14]. From 1991 onward, infants with severe distress or apnea were intubated for a $PaCO_2$ greater than 60 mmHg, and were given surfactant. Twenty-five percent of all infants required only supplemental oxygen and 24% of all infants were ventilated from birth. Fifty-one percent were treated with nasal CPAP, with one-third of these subsequently requiring ventilation. Almost all infants < 24 weeks required ventilation suggesting that this group may require a different approach. Gittermann et al reported that the use of early CPAP for infants < 1500gm (VLBW) significantly reduced the frequency of intubation, reduced mortality ($p=0.038$), and shortened the duration of intubation and length of stay[15]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[16] in a report of 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 reported that there was an increase in the proportion of patients not intubated and mechanically ventilated from 7% to 14% in infants <1000 g and from 28% to 44% in those $\geq$1000 g ($P < 0.02$ and <0.01, respectively). The decrease in intubation was not associated with a significant increase in adverse outcome such as death, intraventricular hemorrhage, periventricular leukomalacia, or BPD. The proportion of infants <1000 g that survived without BPD increased from 38% in 1992 to 48% in 1994; $p < .05$, and the proportion of infants =1000 g in whom BPD developed decreased from 14% to 9%; $p < .05$. None of these observations was from a prospective controlled trial, and in none was there a contemporaneous control group who did not receive early CPAP.

The first prospective trial comparing prophylactic CPAP, started at birth, with conventional management was that of Han et al. They compared the use of nasal CPAP given by nasopharyngeal tube with conventional management in 82 infants, 32 weeks gestational age at birth, and in this study it would appear that CPAP was begun in the DR, but may have been delayed for up to 2 hours.[17] No infants in this trial received surfactant, and no mothers were treated with antenatal steroid. There was no advantage observed with the use of early CPAP, and oxygenation was worse in the early CPAP treated infants. The reviewers of the use of prophylactic CPAP in the Cochrane library concluded that "A multicenter randomized controlled trial comparing prophylactic nasal CPAP with "standard" methods of treatment is needed to clarify its clinical role."[18]

In the post surfactant era, Verder et al conducted the first prospective evaluation of early CPAP (not necessarily delivery room CPAP) and short-term intubation for surfactant administration in a multicenter collaborative trial conducted from September 1991 to October 1992.[19] The primary hypothesis was that the use of early CPAP and brief intubation for surfactant in infants meeting pre-established criteria would reduce the percentage of infants requiring mechanical ventilation from 80% to 40%. Infants randomized to surfactant [Curosurf®] received 200 mg/kg, (2.5 ml/kg) following intubation, with manual ventilation for 2-5 minutes and were then extubated if stable. This study was stopped after an interim analysis demonstrated a significant benefit for the surfactant treated infants. Thirty-three of the 35 infants randomized to early surfactant were extubated after such treatment, and 13 required reintubation at a median of nine hours after surfactant treatment, compared with 28 of 33 control infants who were intubated a median of three hours after randomization, (p=0.003). The overall duration of ventilation in both groups was 2.5 days; there were no other differences between the groups. Verder et al performed a second multicenter prospective trial from April 1995 to January 1997 and enrolled infants <30 weeks with similar criteria to the previous trial, apart from an entry a/A ratio of .35 to .22, which decreased over 30 minutes, which was less stringent, allowing infants to be treated at lesser degrees of oxygen requirement, than their first study. These infants were initially all treated with CPAP and were enrolled up to 72 hours of age (median 4.1 hours, range 0.3 to 40.1hrs).This trial was also stopped after an interim analysis demonstrated a statistically significant reduction in the need for ventilation or death within seven days from 63% in the late-treated infants to 21% in early-treated infants. The median duration of ventilation in both trials was 2.5 days[20]. This study was not a prospective evaluation of early CPAP because CPAP was initiated in all infants at variable ages, and they did not evaluate infants of less than 25 weeks gestation.

Lindner et al recently reviewed their experience using a continuous prolonged (15 seconds duration) pressure controlled (20 to 25 cm H_2O) inflation of the lungs followed by continuous positive airway pressure (CPAP) of 4 to 6 cm H_2O for all ELBW infants immediately after delivery to establish a functional residual capacity (FRC) and to avoid intubation and ventilation[21]. The criteria for subsequent intubation were a $PaCO_2$ > 70 mmHg, an FiO_2 >.6 and respiratory distress with severe recurrent apnea. The rate of early intubation and mechanical ventilation in the delivery room decreased from 84% in 1994 to 40% in 1996. In 1996, 25% of the ELBW infants were never intubated (compared with 7% in 1994). There was no difference in mortality and overall there was less IVH > Grade 2 and BPD for the later cohort. No infant had an air leak upon admission to the NICU, suggesting that use of a prolonged inflation was well tolerated. Only 1 of 11 infants of 24 weeks gestation was able to avoid intubation in this study. Once again, there was no contemporaneous control group who did not receive delivery room CPAP. All of the above studies required high levels of $PaCO_2$ before initiating ventilation for this indication.

There is retrospective evidence suggesting a benefit for early CPAP in experiences from the USA. A survey of eight neonatology units in the USA in 1987 demonstrated that one unit, Columbia, had the lowest rate of CLD[22]. A more recent comparison of practices and outcomes between two neonatology units in Boston and the Babies and Children's Hospital unit (Columbia) evaluated VLBW infants born in 1991 to 1993.[23] This study revealed that 75% of infants at the Boston centers were initially treated with mechanical ventilation compared with 29% at Columbia, whereas initial CPAP was used in 63% of infants at Columbia vs. 11% at the Boston centers. Columbia also used less surfactant, 10% versus 45%, (all $p<0.001$). In addition the rates of CLD were significantly lower at Columbia compared to the other two centers (4% vs. 22%).

de Klerk and de Klerk recently published a five-year retrospective review of the outcome of 1 to 1.5 kg infants (n-116) treated with early CPAP vs. usual care (delayed CPAP)[24]. During 1996 -1998 infants were placed on CPAP within 10 minutes of admission (they did not describe the use of delivery room CPAP). Early CPAP beginning following admission to the neonatal unit decreased endotracheal intubation from 65 to 14%, $p<0.001$ and surfactant use (40 to 12%, $p<0.001$). Ventilator days were reduced from a median of 6 to 2 days ($p<0.01$) and oxygen supplementation or death at 28 days from 16 to 3%, $p<0.05$. Oxygen supplementation or death at 36 weeks did not significantly decrease (11 to 3% $p=0.25$). Ventilation and surfactant use were very high during the delayed CPAP (control period) so it is unclear whether other improvements in care may have coincided with the change to early CPAP.

Sandri et al[25] have recently published preliminary data from a multicenter randomized controlled trial of 155 infants 28 to 31 weeks gestation randomized to CPAP within 30 minutes of birth or to CPAP if the FiO_2 requirement exceeded 40%. Use of surfactant (22 to 21%, NS) and ventilator support (10 to 9%, NS) was not reduced with early CPAP. However, this trial included relatively bigger infants and the control group received CPAP at relatively low FiO_2, minimizing the difference between the experimental and control groups. This study did not evaluate the use of delivery room CPAP.

More recently Thomson et al presented the results of a multicenter trial of 237 infants from 27 to 29 weeks gestation[26], who were randomized to prophylactic surfactant followed by nasal CPAP using the Infant Flow DriverTM, early nasal CPAP followed by rescue surfactant, early IPPV with prophylactic surfactant, and conventional management. They reported that CPAP was initiated by 6 hours of age in 76% and 79% of the first 2 treatment groups, and those infants in the CPAP and rescue surfactant and prophylactic surfactant followed by CPAP groups required the lowest duration of ventilation. There were no differences in the incidence of CLD or other neonatal complications. Neither of these studies instituted the use of CPAP in the delivery room.

In a preliminary feasibility trial we have evaluated the ability of 5 sites of the NICHD Network to initiate CPAP during resuscitation, and continue its use in the NICU. In that study 103 infants were randomized to receive resuscitation with either CPAP/PEEP or no CPAP/PEEP. All infants were treated with CPAP following NICU admission. During delivery room resuscitation, 46 infants were intubated, 27 of 55 CPAP infants and 19 of 48 control infants ($p=0.33$). All 23 week gestation infants were intubated in the delivery room, irrespective of treatment group, whereas only 3 of 22 (13%) infants of 27 weeks required such intubation. When evaluated by birth weight, all 3 infants of less than 500 gm birth weight and 6 of 11 infants between 500-600 gm birth weights were intubated in the delivery room. All remaining infants were admitted to the NICU and had CPAP initiated. For infants not intubated in the DR, 36 infants were subsequently intubated in the NICU by day 7, 16 CPAP infants and 20 Control infants, ($p=0.21$). Infants in the CPAP group developed criteria for intubation sooner than the Control infants, with means and medians of 10.5 and 1.8 hours versus 20.7 and 3.3 hours,

p=0.41. These infants met criteria established for this trial which included an FiO2 > .3 to maintain an SpO2 > 90% or a PaO2 > 45 torr, an arterial PaCO2 > 55-60 with a pH < 7.25. or apnea requiring bag and mask ventilation. CPAP infants were intubated at an average FiO2 = 0.5 compared to 0.4 for control infants.

The literature thus suggests that early CPAP may be of substantial benefit, although none of this information has been obtained from prospective randomized trials of CPAP randomly applied in the delivery room to a population of VLBW or ELBW infants, with an appropriate control group. The terms early CPAP in the above studies (apart from that of Lindner et al[15]) involved the application of CPAP shortly following birth, not immediately after delivery. It is not surprising, therefore, that the recent revised NRP guidelines do not mention the use of CPAP/PEEP for neonatal resuscitation.[27] There is also some evidence that the level of CPAP needed may vary depending on the actual device utilized. Pandit et al and Courtney et al have demonstrated that variable flow CPAP was associated with a lower work of breathing and increased compliance at all levels of CPAP whereas constant flow nasal CPAP increased compliance only at 8 cm H2O.[28] In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.[29] A more recent trial compared the use of variable flow CPAP to conventional CPAP at extubation for 162 ELBW infants and reported no significant differences with either form of CPAP.[30] This study noted that 40% of ELBW infants failed extubation primarily because of apnea.

There are no studies in the surfactant and antenatal steroid era which have prospectively compared delivery room, CPAP with a more conventional approach, such as the use of prophylactic surfactant and conventional ventilation. The current available evidence demonstrates that prophylactic natural surfactant treatment significantly decreases mortality, air leak, and BPD in preterm infants.[31] Early surfactant, defined as surfactant at less than 2 hours of life is also of benefit and reduces air leaks, and mortality.[32] These reviewers noted that "early surfactant administration significantly reduces the risk of key clinical outcomes including pneumothorax, PIE, chronic lung disease, and neonatal mortality. Given the efficacy of prophylactic surfactant therapy (Soll 1999), this meta-analysis suggests that early selective surfactant administration to intubated infants with early signs of RDS may be part of a clinical spectrum of improved outcomes with earlier treatment". The most recent experience regarding early surfactant was presented by Horbar et al at the SPR in May, 2003. Their study which involved a cluster randomization in 57 NICUs of a practice to administer surfactant earlier compared with 57 control NICUs. They noted that infants at the intervention sites received their surfactant more often in the DR (54.7 vs 18.2%, p < 0.001) and earlier than the control sites (21 vs 78 minutes, p <0.001). There were no differences in mortality and pneumothoraces, the intervention centers had a lower rate of overall and severe IVH (28% vs 33%, p < 0.04, 10% vs 14%, p < 0.001) which were secondary outcomes of this trial. [33]

The most recent published study by Tooley and Dyke evaluated the use of prophylactic surfactant and early extubation to CPAP versus prophylactic surfactant and continuing management.[34] In this study 42 infants of 25 to 28(+6) wk of gestation were intubated at birth and given one dose of surfactant. They were then randomized within one hour of birth to either continue with conventional ventilation or to be extubated to nCPAP. They reported that 8 out of 21 (38%) babies randomized to nCPAP did not require subsequent re-ventilation. (Ventilation rates of 62% vs 100%, p = 0.0034). The smallest baby successfully extubated weighed 745 g. There were also significantly fewer infants intubated in the nCPAP group at 72 h of age (47% vs 81%, p = 0.025). There was no significant difference between the two groups in the number of babies that died, developed chronic lung disease or severe intraventricular hemorrhage. This study demonstrates that a significant number of very preterm babies with RDS can be extubated

to nCPAP after receiving one dose of surfactant. The current SUPPORT study will address this population, extended to 24 weeks, using a similar methodology for the infants of 24 to 27 6/7ths weeks who fail initial CPAP, with adequate power to determine if this approach is associated with significant benefits in terms of important short and longer term clinical outcomes.

Oxygen Saturation:

There is now an emerging body of information that suggests that many of the morbid conditions associated with extreme immaturity are potentiated by an excess of free-radicals occurring in infants who are intrinsically deficient in antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase. During hypoxia, metabolic alterations prime hypoxic cells to produce free oxygen radicals when subsequently exposed to oxygen. Such reperfusion injury, in addition to increasing the production of free oxygen radicals, is associated with other metabolic changes which may produce long lasting harmful effects. Silvers et al reported that a low plasma antioxidant activity at birth in premature infants was an independent risk factor for mortality.[35] Pulmonary oxygen toxicity, through the generation of reactive oxygen/nitrogen species in excess-of antioxidant defenses, is believed to be a major contributor to the development of BPD.[363738] For example the preterm macrophage showed a significant increase in cytokine mRNA and protein after overnight incubation in 95% oxygen compared with cells from term animals. Only macrophages from premature animals had a significant increase in intracellular oxygen radical content, measured by 2', 7'-dichlorofluorescin analysis, after incubation in 95% oxygen. This enhanced inflammatory cytokine response to oxygen has been postulated to be a mechanism involved in the early development of chronic lung disease in premature infants.[39] Varsila et al noted that immaturity is the most important factor explaining free radical-mediated pulmonary protein oxidation in premature newborn infants and that oxidation of proteins is related to the development of chronic lung disease.[40]

There are a number of prospective randomized trials that have compared the use of room air with 100% oxygen for neonatal resuscitation, and these have reported Infants resuscitated with room air resumed spontaneous breathing faster and required less positive pressure ventilation than infants resuscitated with oxygen.[41 42] Vento et al also demonstrated that that infants resuscitated with oxygen demonstrated long lasting evidence of oxidative stress and activities of superoxide dismutase and catalase in erythrocytes that were 69% and 78% higher, respectively compared with control infants resuscitated with room air at 28 days of postnatal life.[43] A recent meta-analysis of room air vs 100% oxygen resuscitation comprising of 1,693 infants in five trials revealed decreased neonatal resuscitation in infants resuscitated with room air (6 vs 11%, $p<0.005$ or 0.57 (95% CI 0.40 – 0.81))[44]. While these studies described results of mostly term infants, some infants were premature and the premature infant is known to have decreased antioxidants which would increase their susceptibility to oxygen toxicity. In the only randomized prospective trial to evaluate room air compared with oxygen in preterm infants, Lundstrom et al resuscitated infants of less than 33 weeks gestation who were randomized to receive either 80% oxygen or room air and noted that 2 hours following delivery, the room air infants had a higher cerebral blood flow compared with oxygen resuscitated infants. (median (interquartile range)): 15.9 (13.6-21.9) v 12.2 (10.7-13.8) ml/100 g/minute).[45] They did not find any significant differences in short or long-term outcomes but did note that SpO2 was lower in the room air infants with values at 5 and 7 minutes of 75% and 80% compared with 92% and 94% in the 80% oxygen group ($p<0.001$). Current monitoring with pulse oximetry using limits of 95 to 96% will result in significant periods wherein the infants actual PaO2 may increase to very high levels, as there are rapid increases in PaO2 with very small increments in SpO2 at this plateau portion of the hemoglobin dissociation curve.

Tin et al retrospectively reviewed outcomes for infants admitted to various neonatal intensive care units in northern England from 1990 to 1994 and managed with lower (70-90%) or higher SpO2 ranges (88%-98%).[46] They reported that infants who were managed for at least the first 8 weeks of life with SpO2s from 88-98% developed retinopathy of prematurity severe enough to be treated with cryotherapy four times as often as infants managed with the lower SpO2 ranges. Infants managed with the lower SpO2 ranges did not have increased risk of mortality or neurodevelopmental impairment. Bancalari et al using transcutaneous oxygen monitoring were able to show that infants who received continuous monitoring had a similar incidence of ROP to infants who were monitored by intermittent sampling had similar incidences of ROP, however for subgroup of infants $\geq$ 1100gm, there was a decrease in the incidence of ROP.[47] The STOP-ROP trial randomized infants with already established pre-threshold retinopathy and an SpO2 less than 94% to two ranges of SpO2 (89% to 94% versus 96% to 99%), for at least 2 weeks and until both eyes were at study endpoints. The higher range of SpO2 was associated with a non-significant decrease in the progression of ROP, but was associated with a greater need for oxygen and more exacerbations of BPD.[48]

Chow et al reported their observations following the institution in 1993 of a detailed oxygen management policy that included strict guidelines in the practices of increasing and weaning of fraction of inspired oxygen (FIO2) and the monitoring of oxygen saturation parameters in the delivery room, during in-house transport of infants to the NICU, and throughout hospitalization.[49] The main objectives were to avoid hyperoxia and repeated episodes of hypoxia-hyperoxia in very low birth weight infants. Their approach was initiated at birth, and included the avoidance of repeated increases and decreases of the FIO2, and a change in previously used alarm limits. They reported that following the implementation of these new management strategies that the incidence of ROP Grades 3 to 4 decreased consistently in a 5-year period from 12.5% in 1997 to 2.5% in 2001 and that the need for ROP laser treatment decreased from 4.5% in 1997 to 0% in the last 3 years. They adopted an SpO2 range of 85% to 95% for infants > 32 weeks gestation at birth, and a range of 85% to 93% for infants < 32 weeks. In addition some of their faculty used a range of 83% to 93%. This study did not provide any prospective values of the actual SpO2 ranges that were actually achieved in their infants, and thus it is uncertain whether their observed reductions in ROP were related to the altered SpO2 changes, or to overall changes in management over the period of the study. While these observations are encouraging, the authors did not report the complete neurodevelopmental outcomes for the infants cared for during the period of the new oxygen guidelines, and in the absence of contemporaneous controls, these results cannot be considered as proof that the SpO2 ranges used by this group are beneficial in terms of significant longer -term neurodevelopmental outcomes.

The most recent trial conducted in Australia compared SpO2 ranges of 91% - 94% versus 95% - 98% in 358 infants of less than 30 weeks who remained oxygen dependent at 32 weeks. The primary outcomes were growth and neurodevelopmental measures at a corrected age of 12 months. The high-saturation group received oxygen for a longer period after randomization (median, 40 days vs. 18 days; P<0.001) and had a significantly higher rate of dependence on supplemental oxygen at 36 weeks of postmenstrual age and a significantly higher frequency of home-based oxygen therapy. but resulted in an increased duration of oxygen supplementation.[50] They reported that additional oxygen supplementation did not improve survival, growth, or the occurrence of cerebral palsy at 18 to 24 months. Anderson et al have recently reported the results of a survey of pulse oximetry practices in 142 NICUs in the USA and noted a wide range of monitoring limits from 82% to 100%. They reported a lowered rate of ablative eye surgery in units that used lower maximal SpO2 limits, with the lowest range seen in units that had a maximum SpO2 of < 92%.[51]

In a recent review of oxygen toxicity in the premature infant Weinberger et al recommended that a strategy of limiting oxygen supplementation should be explored to reduce significant morbidities in the premature infant.[52] No studies to date have prospectively randomized ELBW infants to differing oxygenation ranges from birth onwards to determine if there is a benefit of lower versus higher saturation ranges.

1.5 Recent Relevant Studies

We have recently evaluated an FDA approved device specifically designed to facilitate neonatal resuscitation (Neopuff Infant Resuscitator, Fisher and Paykel, Auckland, New Zealand). This device has a t-piece that attaches to a mask and to a simple pressure generator. The inspiratory pressure can be set to a determined level, and a twist valve at the top of the t-piece determines the end-expiratory pressure. Most operators, with the exception of experienced respiratory therapists cannot routinely deliver a predetermined level of positive inspiratory pressures and PEEP[53] using an anesthesia-type manual bag and a neonatal manikin. In contrast, all operators could deliver the predetermined pressures with little intra-individual variation using the Neopuff®. The device operates identically using either a mask or endotracheal tube connection with or without PEEP/CPAP and the operator can adjust the positive inspiratory pressure (PIP) manually during resuscitation. At a flow of 10 liter per minute (lpm) or less, the maximum inadvertent CPAP/PEEP is 0.5 cm H_2O; which does not increase up to rates of 80 breaths per minute, the highest tested rate. The wave form is square, and is more similar to ventilator wave forms than to wave forms obtained using an anesthesia device. It should be noted, that the standard anesthesia devices used in delivery rooms may not deliver the desired CPAP/PEEP, depending on the operator's experience and skill, and may result in overshooting the desired PIP, even when the device is used by experienced operators. The Neopuff® device is now used as the standard resuscitation device in a number of hospitals in the USA, including at least two units in the NICHD Network.

There has been a recent trial evaluating earlier criteria for retinal laser ablative surgery for ROP, the ETROP study.[54] This study has demonstrated that using such criteria the visual outcomes are improved and reported that grating acuity results showed a reduction in unfavorable visual acuity outcomes with earlier treatment, from 19.5% to 14.5% (P=.01)and that unfavorable structural outcomes were reduced from 15.6% to 9.1% (P<.001) at 9 months. They recommend retinal ablative therapy for eyes with type I ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph); zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 ROP with plus disease. While these results are likely to be integrated into Network practice, there is currently no baseline data regarding the number of infants who would meet these criteria, and thus we will utilize the presence of Stage 3 or greater ROP and/or the receipt of retinal surgery to power our current trial.

2.1 Study Design

This will be a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. The individual factors to be tested will be:

1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early ($\leq$ 1 hour) surfactant and mechanical ventilation.

2) A prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant is no longer requiring ventilatory support

or oxygen.

The oxygen saturation monitoring portion of our study will be designed to parallel the planned POST-ROP trial, a multicenter, multinational prospective trial to evaluate different SpO2 levels from birth.[55] The methodology described under oxygen monitoring (**Section 4.1B**) was developed for the current protocol to allow a blinded comparison of 2 different SpO2 levels using specially designed pulse oximeters. These devices have been developed by the Masimo Corporation (Irvine Ca) and tested prior to initiation of this trial, and the POST-ROP study group has agreed to use the ranges described in this protocol, and the methodology that will allow the oximeters to provide actual SpO2 values when the SpO2 is < 85% and > 95%(Personal communication, Cynthia Cole 2004). This methodology will provide the clinicians and caretakers with the infants' actual SpO2 values during hypoxia and hyperoxia, within the current parameters of clinically accepted practice.

Please see **Section 8.2** for further Tables describing details regarding the projected outcomes relative to the study interventions

Randomized Intervention	**Low SpO2 85% to 89%**	**High SpO2 91 to 95%**
Treatment **Early CPAP**	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control **Prophylactic/Early Surfactant**	Control + Low SpO2	Control + High SpO2

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

2). We hypothesize that that relative to infants managed with a higher SpO2 range that the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

2.3 Secondary Hypotheses

We hypothesize that the use of continuous positive airway pressure (CPAP) with a permissive ventilator strategy and/or a lower SpO2 range starting at birth in the delivery room will result in the following:

- A decreased Mortality/NDI at 18-22 months corrected age.

- A decreased frequency of endotracheal intubation before 10 minutes of age
- A decrease of the total duration of mechanical ventilation during the entire NICU stay
- A decreased incidence of surfactant treatment
- A decreased incidence of air leaks on admission and overall
- A decreased duration of intubation
- A decreased duration of mechanical ventilation
- A decreased duration of oxygen supplementation
- A decreased duration of the percentage of pulse oximetry values > 90%
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- A decrease in the percentage of infants who receive postnatal steroids to prevent or treat BPD
- A decreased incidence of BPD at 36 weeks using the physiologic definition of BPD
- A decreased incidence of ROP or Stage 3 ROP
- A decreased incidence of necrotizing enterocolitis (NEC)
- A decreased incidence of IVH and severe IVH
- A decreased incidence of periventricular leukomalacia
- A decreased incidence of neurodevelopmental impairment at 18-22 month follow-up
- A decreased incidence of cerebral palsy at 18-22 month follow-up

3.1 Study Population

Study subjects are infants of 24 0/7ths to 27 6/7th weeks at birth for which a decision has been made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) will be enrolled because over 80% of such infants in the Network are intubated, usually early in their neonatal course. It is important to note that previous studies have included few, if any infants less than 25 weeks gestation and such infants are not included in the current COIN trial or the proposed Vermont Oxford Trial. Such infants will be enrolled in this trial because they are the group of infants with the highest mortality and morbidity. The feasibility trial demonstrated that the 5 NICHD centers involved could reduce intubation in the delivery room to less than 50% of such infants if they are not intubated for surfactant. We will exclude infants of 23 weeks or less in view of their extremely high mortality and morbidity, and their almost universal need for delivery room intubation for resuscitation. We have included Tables at the end of the protocol utilizing infants from 23 to 28 weeks to demonstrate that our sample size estimates will not be adversely affected if we should choose to include infants of 23 and/or 28 weeks.

Strata: There will be 2 randomization strata, infants of 24 0/7ths to 25 6/7ths weeks, and infants of 26 0/7ths-27 6/7ths weeks by best obstetrical estimate. The purpose of stratification is to assure an appropriate distribution of risk among the four study arms. The study will not be powered to detect outcome differences between strata.

3.2 Inclusion Criteria

- Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
- Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Infants whose parents/legal guardians have provided consent for enrollment, or
- Infants without known major congenital malformations

3.3 Exclusion Criteria

- Any infant transported to the center after delivery
- Infants whose parents/legal guardians refuse consent
- Infants born during a time when the research apparatus/study personnel are not available
- Infants < 24 weeks 0 days or ≥ 28 weeks 0 days, completed weeks of gestation

3.4 Sampling Recruitment and Screening Procedures

Infants will be recruited for this study by approaching one or both parents at the time of admission to the hospital where there is deemed to be a risk of premature delivery at 27 6/7ths weeks or less.

3.5 Screening Procedures

All admissions for threatened premature delivery will be screened on a daily basis to ensure that eligible patients can be enrolled. We will inform our obstetrical colleagues at each involved institution of the nature of this study, and encourage them to discuss this study with their patients at risk of premature delivery. The study coordinator at each site will maintain a screening log of potentially eligible patients. In addition the usual practice of neonatal consultation for all such at risk deliveries will provide a second opportunity to approach mothers with fetuses at risk of preterm delivery

3.6 Other Procedures

A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology will be used at all sites for the delivery room administration of CPAP. A training video to explain the proper use of the Neopuff® will be provided to any site which wishes to use it and is not familiar with the device.

3.7 Randomization

Randomization will be stratified by gestational age group, will occur prior to delivery for consented deliveries, and will be performed by utilizing specially prepared double-sealed envelopes. Deliveries will be randomized as a unit, thus multiples, twins, triplets etc will be randomized to the same arm of the trial. We believe that this methodology will improve the percentage of consents, since in previous trials parents of multiple infants have expressed concern that their infants were being randomized to different treatment arms. We have made an appropriate sample size adjustment to account for this clustering effect.

Each randomization will indicate either Treatment Group (CPAP and permissive ventilation management) or Control Group (Prophylactic/Early surfactant and conventional ventilator management) and either the Low (85%-89%) or High (91% - 95%) SpO2 group. Parents will be approached for consent before delivery, but the randomization envelope will only be opened when delivery is imminent for a consented family.

The Pulse Oximeters (PO) will have unique identifying labels and the oximeter specified in the randomization will be identified by a unique number which will match the number of the study Pulse Oximeter assigned for that infant. All caretakers including the coordinators will be blinded to the Pulse Oximeter range, and an identification code for each site will be maintained by the PI/Site Coordinator should identification be required for patient safety. RTI will work with Masimo to ensure that the POs are labeled with unique identifiers, whose code will identify the

actual range of the individual PO. These would be affixed prior to shipping to the sites, and a copy of the labels sent to the site would be provided to RTI.

This methodology should reduce the work load to the sites at the time of randomization, providing the care team with the information needed for the infants' randomization, and will allow the study center to be notified within 24 hours of any randomization.

3.8 Informed Consent:

Parents will be approached prior to delivery for informed consent, and their infants enrolled at delivery. As previously noted we will randomize by family, thus all offspring will be randomized to the same trial arms, provided adequate equipment and personnel are available at the time of delivery.

3.9 Management and Retention of Study Population

All enrolled infants will be seen at follow-up-up at 18 to 22 months corrected age. We do not anticipate a significant loss other than death (13% in the first 12 hours , approximately 32% before discharge, based on year 2000 registry data), and will plan for a further 15% attrition.

4.1 A: Study Intervention: Mode of Ventilatory Support

The intervention will begin after birth when the infant is given to the resuscitation team. The conduct of the resuscitation will follow usual guidelines, and once stabilized, all Control infants in both strata will receive prophylactic/early surfactant (within 1 hour of age) whereas all Treatment infants will be placed on CPAP/PEEP following stabilization, and be intubated only for resuscitation indications.

The assignment to either a high or low SpO2 by study oximeter assignment will be performed immediately following NICU admission, with a maximum allowable delay of 2 hours following NICU admission.

TREATMENT: CPAP Group : Early Extubation and CPAP

Delivery Room Management

FiO2:

Standard of care.

CPAP:

CPAP or ventilation with PEEP will be utilized if the infant requires positive pressure during resuscitation. CPAP will be continued until admission to the NICU using the Neopuff or equivalent device and a face mask or nasal prongs. Initial PPV will be at a PIP of 15-25 cm H_2O and a PEEP/CPAP of 5 cm cmH_2O.

Intubation:

Infants may not be intubated for surfactant only in the DR. Infants who require intubation for resuscitation will receive surfactant within 60 minutes of birth.
Intubation will be performed only for the standard NRP indications including failure to respond to PPV with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determines that surfactant is urgently required.

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

NICU Management

These infants will be managed on nasal CPAP, and intubation is never required by protocol. They *MAY* be intubated if they meet ***ANY*** *of* the criteria listed below. If intubated within the first 48 hours of life they should receive surfactant

Intubation:

- An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) documented on a single blood gas within 1 hour of intubation
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation.)

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

These criteria will continue in effect for a minimum of 14 days of life.

Intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.
(e.g. - Upper airway obstruction (choanal atresia, micrognathia/glossoptosis)).

Extubation:

An intubated CPAP-Treatment infant ***MUST*** *have extubation attempted within 24 hours if* **ALL** *of the following criteria are met and documented on a single blood gas*

- $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples)
- An indicated SpO2 $\geq$ 88% with an FiO2 $\leq$ 50%
- A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving ionotropic/vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA

These criteria will continue in effect for the first 14 days of life.

Failure to extubate an infant meeting all of the above criteria will be recorded as a study protocol violation unless extenuating circumstances are noted. (e.g. - PIE, airleak)

Reintubation

If a Treatment infant is extubated as per Protocol Criteria, and requires re-intubation for any indication, any further attempt at extubation may be delayed for 24 – 48 hrs based on the clinician's decision.
Re-intubation criteria are the same as those for Intubation for the CPAP infants. Thus, intubation is not required, but these infants **MAY** be reintubated if they meet **ANY** of the following:

Re-Intubation Criteria:

- An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) for 2 successive blood gases at least 15 minutes apart.
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation as noted above on page 13)

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Re-intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.

D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be discontinued earlier and follow unit Standard of Care. CPAP may be restarted at any time in such infants.

CPAP infants who require intubation three times, for any criteria, will have all subsequent treatment including subsequent extubations and any further re-intubations performed using unit Standard of Care. This addition is to prevent such infants from being exposed to further protocol driven intubations and extubations.

Surfactant

Infants intubated in the first 48 hours for respiratory distress should be given a minimum of one dose of surfactant
Up to 4 surfactant administrations may be given if the FiO2 is greater than 50% following manufacturers' recommendations for dose and dosing interval.

Explanation:

The purpose of the above criteria is to minimize the duration of intubation of Treatment infants. The Criteria for extubation are more severe than those of the Control Group infants, and extubation must be attempted for any infant who fulfills the stated criteria.

The criteria for re-intubation recognize that intubation is traumatic, and is designed to avoid frequent attempts at extubation for infants who fail.

CONTROL - Prophylactic/Early Surfactant and Ventilation

Delivery Room Management:

Infants will be intubated in the delivery room and given surfactant or receive surfactant

within 60 min minutes of birth. The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

NICU Management:

***Extubation*:**

An intubated Surfactant-Control infant will continue to receive mechanical ventilation until extubation criteria are satisfied, but **MUST** have Extubation attempted within 24 hours of fulfilling ***ALL*** of the following criteria documented on a single blood gas.

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 = 35 with a SpO2 > 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving ionotropic / vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA (Defined as bounding pulses, audible murmur and Echo confirmation of L-R shunting with increased LA/Ao size

These criteria will continue in effect for a minimum of 14 days for all infants.

Failure to attempt to extubate an infant meeting all of the above criteria, or extubation prior to reaching criteria, will be recorded as a study protocol violation unless extenuating circumstances are noted.

Weaning

This protocol will not define strict weaning criteria for the Control infants, but it is to be understood that reasonable attempts should be made to extubate these infants. While it is understood that some centers may be using somewhat more severe FiO2 and PaCO2 criteria than those listed here as current practice, these Criteria are thought to reflect current Network practice and practice at 2 of the 3 Best practice centers.

Reintubation:

- Control Infants may be reintubated using Standard of Care.

Explanation:

Control infants are to be treated using an approach considered similar to current standards of care. Apparatus for resuscitation for Control Infants at each center will represent their usual equipment for the resuscitation of an ELBW infant. The Neopuff may be utilized for such infants as above, but this is not mandatory. It is anticipated that the majority of these infants will be intubated and receive surfactant in the delivery room.

4.1 B: Study Intervention: Low versus High SpO2 Range:

There will be 2 ranges of SpO2 utilized during this trial. The Low target range will be 85% to 89% and the High target range will be 91% to 95%. The altered Pulse Oximeters (PO) are described below, and will display a range of 88% to 92% when the SpO2 ranges are in the Target ranges indicated above. Thus a Low range PO will read 88% when the actual SpO2 is

approximately 86%, and 92% when the actual SpO2 is 89%. Similarly the High range PO will display 88% when the actual SpO2 is 91% and indicate 92% when the actual SpO2 is approximately 95%. See below for further explanation. This deviation is similar to the BOOST trial which used a continuous 3% offset.[42] As an added safety feature, the POs used in this trial will revert to the actual SpO2 values and allow the caretakers to be aware of actual SpO2 values < 85% and > 95%.

Low Range Infants:

These infants will be monitored with a target SpO2 range of 85% -89% with suggested indicated alarm limits of 85% and 95%, representing approximately a 10% span for alarms as long as the infants are receiving any ventilatory support, CPAP, and/or supplemental oxygen. **The study pulse oximeters will be applied to the infant within two hours following NICU admission.** The assigned PO will remain on the infant and will be removed once the infant has been in room air and off ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA.

High Range Infants:

These infants will be monitored with a target SpO2 range of 91% -95% with suggested indicated alarm limits of 85% to 95% representing approximately 10% span for alarms as long as they are receiving any ventilatory support, CPAP and/or supplemental oxygen. The study pulse oximeters will be removed once the infant has been in room air for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA.

These interventions will be delivered using specially developed pulse oximeters whose displays (the actual readings seen by caretakers) will be adjusted so that the randomized range of SpO2 (either 85%-89%, or 91%-95%) will be indicated by a range of 88%-92%. This is done by progressively altering the offset as the alarm limits are approached, and Masimo has confirmed that this technology is workable. The target oxygen saturation (88-92%) of the display will be the same in both groups as indicated in Table1 below.

These POs will be able to display trend plots of the SpO2 display for a preceding interval to allow the caretakers to receive feedback regarding the actual SpO2 ranges of their baby.

The suggested alarms limits will be 84% and 96% for both groups.

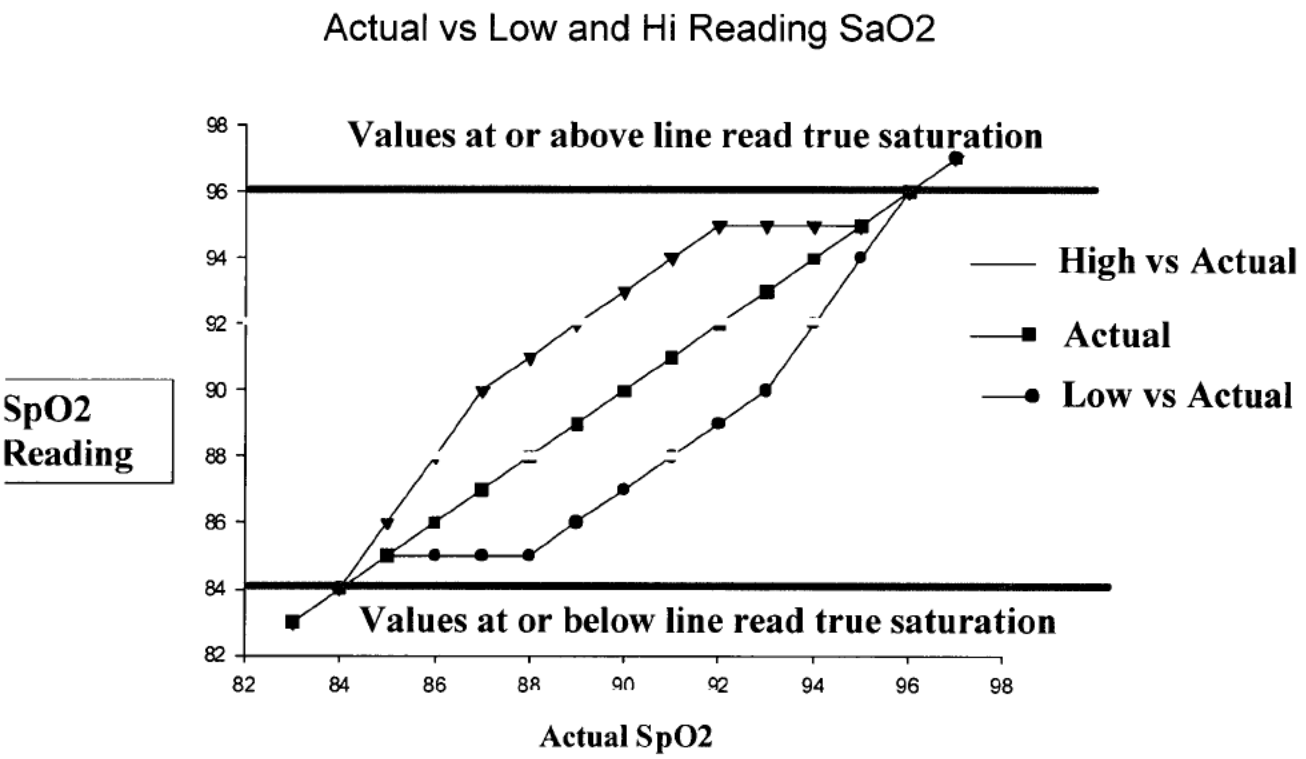
Table 1. Output and Actual SpO2 Targets and Alarms

SpO2 Group	Displayed Target	Actual Target	Alarm Values
Low SpO2	88-92%	85-89%	<85 and >95%
High SpO2	88-92%	91-95%	<85 and >95%

The pulse oximeters will display the actual reading when then the SpO2 is below 85% and above 95%. This will provide for an overall set of limits on actual SpO2 of 84% to 96% which we believe will avoid unacceptable levels of hypoxia, (< 85%) and hyperoxia (> 95%) **All data below 85% and above 95% will be unaltered on all oximeters**. An averaging time of 16 seconds will be applied in keeping with the settings used by POST-ROP. The preset alarm

delay will be 10 seconds. The fail-safe alarm will alarm whenever the reading is 5% below the low alarm limit, in the study this will be at 80%. Some network centers use an averaging interval of 30 seconds, others use very short averaging times. This setting will allow for appropriate response times without unmasking the caretakers.

We believe that this methodology will provide an acceptable ethical design for this trial. The diagram below demonstrates how the pulse oximeter readings are altered between values of 85% to 95%. Readings below or above these levels will not be altered, and will represent actual SpO2 as determined by the pulse oximeter. Note that the entire range of actual SpO2 is altered to either a lower (Low SpO2 Group) value or higher value (High SpO2 Group) till the ends of the alarm ranges of 85% and 95% which will ensure that the infants SpO2 will be separated throughout this range.



Every 30 days until 36 weeks PCA or until the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per 10 seconds of monitoring) will be downloaded and transmitted to RTI for subsequent analyses. (This interval of sampling may change to a less frequent interval for the convenience of the study personnel, without losing significant data). These data points will be used to confirm that the infants were managed at the target ranges and provide objective confirmation of the SpO2 Group assignments. The technology for downloading and interpreting this data was used in the DR CPAP Pilot trial, but recent technology utilizing a software program (Profox, Profox Inc, Escondido, Ca) which has been written to facilitate this process, will dramatically simplify this procedure.

Non-study pulse oximeters cannot be used on enrolled patients. If a second oximeter is

required for such a patient, the site coordinator will provide an identical oximeter for the patient.

All ventilatory care after 14 days of age will follow the standard of care for each unit. Each unit will provide guidelines for their approach to continuing mechanical ventilation.

4.2 Delivery of Interventions

CPAP/PEEP in the DR

CPAP and positive pressure ventilation (PPV) in the delivery room for Treatment infants will be administered via a T-piece resuscitator, a neonatal ventilator or an equivalent device that is currently used by the site for the delivery of CPAP. (See **3.6**).

Use of Nasal SIMV;

This approach is currently used by some Network units and has been previously established as being superior to CPAP following extubation in three prospective trials.[56,57,58] For uniformity nasal SIMV may be used in place of CPAP ***only following extubation for both Treatment and Control infants.***

Use of Caffeine:

Caffeine may be administered 2 hours prior to planned extubation, and for any clinically significant apnea.[59]

Surfactant Type:

All centers are asked to follow current unit practice in determining the type of surfactant utilized, and manufacturers' recommendations for redosing intervals.

The protocol requires that at least one dose of surfactant be administered to any infant intubated within 48 hours of birth, with evidence of respiratory distress, who has not previously received surfactant.:

Postnatal Steroids

Postnatal steroids for the purpose of preventing or treating BPD/CLD will be prohibited for any infant in this trial in the first 21 days of life. Hydrocortisone for hypotension may be used as noted below.

If postnatal steroid use is considered after 21 days of life for any infant for the prevention/treatment of established lung disease the following guidelines should be followed:

1. The AAP statement and recommendations regarding Post-natal steroids should be adhered to.[60]
2. The lowest dose of dexamethasone considered effective should be used and if ineffective after 24 – 48 hours they should be stopped.
3. Consider using hydrocortisone as a first therapy at a dose of 1 -2 mg/kg/day before using dexamethasone.
4. For hypotension, hydrocortisone in a dose of 1 mg/kg/dose should be given after fluid administration and standard doses of ionotropes/pressors have failed to correct the low blood pressure.

Head Ultrasound

If a Head ultrasound is done between days 4 and 21 the results will be recorded for this study. If one is not done for standard of care, the study requires that at least one HUS be completed during this window

4.3 Protocol Violations:

The occurrence of any one of the following criteria will determine whether an individual infant will be considered a protocol violation:

1. Intubation of a treatment group infant in the DR for the exclusive purpose of giving surfactant, in the absence of bradycardia (HR< 100 bpm) and/or poor color or an SpO2< 85-90% in an infant with adequate spontaneous respirations or receiving adequate ventilation
2. Failure to continue CPAP on admission to the NICU for a treatment infant requiring supplemental oxygen
3. Intubation and surfactant administration of a treatment infant without meeting stated protocol criteria.
4. Failure to extubate a Treatment infant who fulfills all the extubation criteria.
5. Extubation of a Control infant who does not meet any of the Extubation criteria.

All protocol violations will be reviewed by the center PI who will discuss each protocol violation with the involved clinicians and provide a written summary including steps taken to avoid future violations.

4.4 Adverse Events

Serious and unanticipated adverse events may be anticipated in this vulnerable population. Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

These outcomes will be evaluated on a monthly basis by RTI, and if the incidence of any of these outcomes is determined to be 5% - 10% greater in any arm of the study, this information will be provided to the Study PI and committee and the DSMC for immediate consideration, and evaluated for consideration of termination of the study or treatment arm.

4.5 Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. Obrien-Fleming [61] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock [62] boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

5.1 Measurement Methods:

The PO stored data will be retrieved using a routine provided to all site coordinators, and the resultant data file will be sent electronically to RTI to be included as part of the study data collection.

5.2 Schedule of Data Collection: (See Data tables in Appendix A)

5.3 Primary and Secondary Outcome Measures

5.3.1 Primary Outcome Measure

The primary outcome will be the percentage of infants surviving without BPD (using the Physiologic Definition) or severe ROP (threshold disease or the need for surgery).

5.3.2 Secondary Outcome Measures

- The five minute Apgar score
- The percentage of infants with death or neurodevelopmental impairment at 18 months
- The total duration of mechanical ventilation during the entire NICU stay
- The percent of infants alive and off ventilation by day 7
- The proportion of infants receiving surfactant treatment
- The incidence of air leaks on admission and overall
- The incidence of BPD at 36 weeks using the physiologic definition of BPD
- The incidence of death
- The proportion of infants with severe IVH
- The proportion of infants with PVL
- The proportion of infants with threshold ROP and requiring surgery for ROP
- The proportion of infants requiring endotracheal intubation before 10 minutes of age
- The proportion of infants with of air leaks on admission and overall
- The duration of oxygen supplementation
- The percentage of pulse oximetry values > 90%
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- The proportion of infants who receive postnatal steroids to prevent or treat BPD
- The proportion of infants with who develop necrotizing enterocolitis (NEC)
- The proportion of infants with cerebral palsy at 18-22 month follow-up

6.1 Training Study Personnel

6.1.1 Job Descriptions of Study Personnel

The NICHD coordinators will assist the respiratory therapists in each unit regarding the set up the equipment for the delivery of CPAP in the delivery room, and in the NICU.

6.1.2 Training of Personnel

There will be a training session held in Cincinnati about the delivery of CPAP in the delivery room and in the NICU, and a review of available devices that may be used for this intervention.

7.1 Data Collection and Management

We will develop the required CRFs as per Network procedures. It will be our aim to minimize these to ensure that data is collected regarding the intervention, the adherence to the protocol for intubation, surfactant administration, and extubation, and the occurrence of the primary and secondary end-points. All remaining information will be extracted for the current data forms.

8.1 Statistical Analysis

8.1.1 Analysis Plan

The primary analyses of this factorial trial will be a logistic regression analysis of the percent of each Group (Treatment vs Control, High vs Low SpO2) who developed their respective outcome measure (survival without BPD or ROP at 36 weeks respectively). An important analysis of a secondary outcome will determine if there is an effect of the interventions on the percent infants who survive without neurodevelopmental sequelae at 2 years For all secondary outcomes, univariate analysis for continuous variables will be performed using parametric (e.g., Student t tests, ANOVA), and non-parametric (e.g., Mann-Whitney U) tests where appropriate; categorical variables including the primary outcome, feasibility, will be examined by Chi square analysis. Analysis of covariance and multiple regression models will be used to examine the interaction between, and the independent effects of, various factors, (e.g., birth weight, gestational age, gender, treatment group, center, etc.) upon secondary outcomes (i.e., time to improvement in oxygen saturation, duration of positive pressure ventilation, five minute Apgar score, duration of mechanical ventilation, surfactant requirement, incidence of air leaks, and incidence of BPD).

8.2 Sample Size

As discussed above, there are two main outcomes for the factorial design: mortality or BPD; mortality or ROP. Mortality or NDI is a secondary outcome. For the cohort of infants born in 2000, 401-1000g birth weight, we have the following prevalence of outcomes for four subgroups of that cohort: Please note that we used population groupings to include or exclude infants of 23 and 28 weeks. These additional groups do not change the sample size estimates as the outcomes are essentially similar.

Subgroup	Death/BPD	Death/> Stage III ROP	Death/NDI
23-27 GA	70.6	53.1	65.7
24-28 GA	64.8	44.5	59.3
24-27 GA	66.6	46.8	60.7
23-28 GA	68.6	50.4	64.0

If the study is powered for the two outcomes, Death/BPD and Death/>Stage III ROP, then the sample size is driven by the prevalence nearest 50% for a given absolute percentage detectable change in the outcome. In this case it's the Death/>Stage III ROP outcome with a range of 44.5% to 53.1% across the subgroups. Furthermore, the sample size depends on the outcome rate only through the standard deviation of the rate and this turns out to be essentially

50% for all subgroups (i.e. ranges from 49.7% to 50.0%). Hence one sample size table suffices for all.

Hence, for any of the four groups the table below gives the total sample sizes required for a range of absolute percent changes, a two-tailed alpha level test of 5% and for powers of 80% and 90%. The N1 column powers the 2 x 2 factorial for the two primary outcomes and the N2 column assures comparable power for the Death/NDI outcome.

With regard to the power for detecting the interaction between the two factors in the factorial, a fourfold increase in the stated sample size would be required to detect an interaction effect as large or larger as that stated in the table (i.e. the Detectable Difference), assuming the same alpha level and power. The interaction effect referred to is the classical one where the difference in outcome for one of the treatments in the factorial differs according to the level of the other treatment (i.e. the treatment effects are not additive).

If the study is powered for the two primary outcomes and mortality/NDI is considered as a secondary outcome then the table below gives the total sample size required for a 5% overall level test at 80% and 90% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and a conservative outcome rate of 50% in making the calculations. These sample sizes are given in the N1 column and would also allow a 10% difference in NDI/death to be detected with a power of 73%. If an 80% power is desired for the NDI/mortality outcome this would result in sample sizes in the N2 column.

TOTAL SAMPLE SIZES REQUIRED

	80% Power		90% Power	
Detectable Difference (absolute %)	Total N1*	Total N2**	Total N1*	Total N2**
8%	1792	2096	2284	2676
9%	1388	1624	1792	2096
10% (multiples to same arm)	1120	1312	1456	1704
11%	940	1104	1208	1416
12%	784	920	1032	1208
13%	672	788	860	1008
14%	584	680	756	880
15%	504	588	652	768

* sample sizes to insure the appropriate power for the two primary outcomes (BPD/Death, ROP/Death)
** sample sizes to insure the appropriate power for the secondary outcome (NDI/Death)

We have increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduces a clustering effect into the design. The analysis of the GDB data base resulted in the 1.12 estimate. We also inflated the sample sizes by 17% to adjust for attrition after discharge and before follow-up. This figure was also determined from the GDB data base. Thus the actual sample size for this trial would be 1310 for 80% power for detecting an absolute difference of 10% in the two primary outcomes and the NDI secondary outcome. This sample size is not sufficient to permit detection of interactive effects between the two treatments with reasonable power.

HYPOTHESIZED TREATMENT EFFECTS FOR SUPPORT

When sample sizes were estimated for the SUPPORT trial the following base rates for the three outcomes (rounded) were calculated from the GDB:

--BPD/Mortality—67%
--ROP $\geq$ Grade III/Mortality—47%
--NDI/Mortality—61%.

Sample sizes were calculated for a range of absolute treatment effects and 10% seemed to be the smallest plausible effect for the study. Rounding the above rates to 65, 45, and 60 percent the following tables show what the data would look like under the assumption of a 10% reduction in outcome and control rates of 65, 45, and 60 percent for the DRCPAP (No)/ SpO2 (High) group. Interactive effects are assumed to be zero. Tables are presented which show treatment effects when both treatments affect the BPD and the ROP outcomes and when only one of the treatments affects outcome. The NDI table is only for the case where both treatments affect outcome.

Table IA

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on BPD/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO2

CPAP	Low	High	Overall
Yes	45	55	50
No	55	65	60
Overall	50	60	55

Table IB

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on BPD/Mortality **Assuming a 10% Main Effect for CPAP Only**—Table Entries are Outcome Rates (%)

SpO2

CPAP	Low	High	Overall
Yes	55	55	55
No	65	65	65
Overall	60	60	60

Table IIA

Treatment Effects for SpO2 (High, Low) and DRCPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO2

SpO2

CPAP	Low	High	Overall
Yes	25	35	30
No	35	45	40
Overall	30	40	35

Table IIB

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for SpO2 Only**—Table Entries are Outcome Rates (%)

		SpO2		
		Low	High	Overall
CPAP	Yes	35	45	40
	No	35	45	40
	Overall	35	45	40

Table III

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on NDI/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

		SpO2		
		Low	High	Overall
CPAP	Yes	40	50	45
	No	50	60	55
	Overall	45	55	50

9.1 Quality Control

The selection of personnel will be left to the site PI's. No specific job descriptions are required for this protocol. The actual duties of the individual who will perform the randomization will be detailed in the manual for the study. Protocol violations will be reviewed, and if frequent, may require a site visit and consideration for termination of a collaborating site.

10.1 Risks and Benefits

Potential risks to the use of CPAP and/or PEEP include pneumothoraces; however this is unlikely to be increased over the risk of PPV alone. The level of CPAP/PEEP will be set at 5-6 cmH_2O, a level that is not thought to increase the incidence of pneumothorax. Recent data from Dr Morley suggest that this level is probably the lowest effective level especially when the infant's mouth is open, and is well tolerated. Objections to use of PEEP or CPAP could be countered by the argument that the majority of neonatologists use PEEP in resuscitation, thus the standard of care at most centers probably include the administration of CPAP and/or PEEP. Another potential risk is the administration of CPAP in the DR to infants without respiratory distress, which could conceivably cause vagal stimulation and resultant bradycardia and gastric distension.

Perhaps the major risk of this trial is that the known benefit of early surfactant with a reduction of death and disease severity, and a reduction of BPD with natural surfactant may not be offset by the early use of CPAP. However, the increasing trend in the use of early CPAP without such evidence represents an even greater risk.

Appendix A

Study Tables

Table 1. Patient Description

	Treatment	Control	P Value
Birth weight (grams) (M + SD)			
Gestation (weeks) (M + SD)			
Apgar 1 min < 3 Assigned			
Apgar 5 min < 3 Assigned			
Received PPV (Number, %)			
Surfactant in DR (Number, %)			
Received Chest Compression (N%)			
Received Epinephrine (N, %)			

Table 2. Other Outcomes

	Treatment	Control	P Value
Total Duration of Mechanical Vent (M +SD)			
Duration of Oxygen (Total days)			
Duration of CPAP			
Duration of nSIMV			
% alive off MV by Day 7 (+SD)			
Pneumothoraces (N, %)			
Other air leaks (N, %)			
BPD at 36 weeks (O_2 dependence)			
BPD by Physiologic Definition (N%+SD)			
Survived to discharge (N,% +SD)			
Number Never Intubated (N, %)			
Number receiving PNS for BPD (N, % %)			
Alive without neurdevelopmental impairment at (18-22 months) years (N, %, +/-SD)			

Appendix B

Study Tables

Table 1. Patient Description

	Low Saturation	High Saturation	RR	CI	p value
Birth weight (grams) (M + SD)					
Gestation (weeks) (M + SD)					
Race (W, B, H, other) %					
Antenatal steroids (%)					
Apgars ≤3 at 5 min					

Table 2. Primary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Threshold ROP/Surgery or death by 36 weeks (%)					
Death by 36 weeks (%)					
Threshold ROP in alive infants at 36 weeks (%)					
BPD or Death by 36 weeks (%) ±					

Table 3. Secondary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Death by discharge status (%)					
BPD in alive infants at 36 weeks (%)					
IVH 3 or 4/PVL or death by 36 weeks (%)					
IVH 3 or 4 in alive infants at 36 weeks (%)†					
Cystic PVL in alive infants at 36 weeks (%)†					
Neurodevelopmental impairment or death by 18-22 months (%)					
Death by 18-22 months (%)					
Neurodevelopmental impairment at 18-22 months (%)†					
Cerebral palsy at 18-22 months (%)†					
MDI < 70 (%)					
PDI < 70 (%)					
Any blindness at 18-22 months (%)†					
Unilateral blindness at 18-22 months (%)†					
Deafness at 18-22 months†					

†Analyzed for survivors

Table 4. Other Outcomes

	Low Saturation	High Saturation	RR CI	P Value
Total Duration of Ventilation (M+SD)				
On ventilator or death by day 7 (%)				
Pneumothorax (%)				
Any air leak (%)				
Postnatal steroids for BPD (%)				
Necrotizing enterocolitis ≥2 (%)				
PDA requiring surgery				

	Early CPAP/Early Extubation	Prophylactic Surfactant
Delivery Room Management	Resuscitate using CPAP. If necessary, initial PPV settings PIP 15-25, PEEP 5. Transport on CPAP If intubated for resuscitation, give surfactant within 1 hour of age. Do not intubate unless indicated by NRP guidelines	Intubate and give surfactant within 1 hour of age Transport with PPV according to SOC
Upon NICU Admission	Randomize within 2 hours to Pulse Oximeter	Randomize within 2 hours to Pulse Oximeter
Intubation Criteria	**Not Required. May intubate for ANY of these criteria** • FiO_2 >.50 required to maintain indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour • $PaCO_2$ > 65 torr (art. or cap. samples, if venous $PaCO_2$ > 70 torr) documented on a single blood gas • Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. **If intubated, give surfactant within the first 48 hrs if in respiratory distress**	**Reintubation Criteria** **Standard of Care**
Extubation Criteria	**Attempt extubation within 24 hours of fulfilling all of the following criteria:** • $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples) • An indicated SpO2 $\geq$ 88% with an FiO2 $\leq$ 50% • Mean airway pressure (MAP) < 10 cm H_2O, vent rate $\leq$ 20 bpm, amplitude < 2X MAP if on HFV • Absence of clinically significant PDA • Hemodynamically stable	**Keep intubated and ventilated until criteria met. Attempt extubation within 24 hours of fulfilling all of the following criteria** • $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples) • FiO2 $\leq$ 35 with SpO2 > 88% • Mean airway pressure (MAP) < 8 cm H_2O, vent. rate $\leq$ 20 bpm, amplitude < 2X MAP on HFV • Absence of clinically significant PDA • Hemodynamically stable
Repeated Surf Doses	Subsequent doses may be given at the manufacturer's recommended dose up to a total of 4 doses.	
Intubation	Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery	
CPAP D/C	In room air for at least 1 hour	
CPAP Resumption	At any time	
Duration of Intervention	14 days	14 days

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From: Higgins, Rosemary (NIH/NICHD)
To: Susan Hintz
Subject: RE: SUPPORT MRI Secondary
Date: Wednesday, December 29, 2004 2:48:00 PM

We anticipated 10-20% deaths and rate of 90% enrolment at Houston, Stanford. 70% enrollment at the other sites (may be too optimisitic). The total n for support is 1300-1400.
Hanks
Rose

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wednesday, December 29, 2004 2:52 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT MRI Secondary

Is that 577 patients initially enrolled in SUPPORT, or alive at 35-42 weeks? If it is enrolled, then I would still have 80% power with alpha of 0.01 to detect at change of about 35% in the outcome of death/abnormal MRI result between groups. If it is alive at 35-42 weeks - that's a pretty big number! More than I was expecting. What rate of death before discharge are you using?

Thanks

Susan

> Susan
>
> I have calculated approximately 577 patients would be available - does that sound reasonable?
> Thanks
>
> Rose

> **From:** Susan Hintz [mailto:srhintz@stanford.edu]
> **Sent:** Wednesday, December 29, 2004 12:50 PM
> **To:** Higgins, Rosemary (NIH/NICHD)
> **Subject:** RE: SUPPORT MRI Secondary
>
> I would assume 90% of survivors from Houston and Stanford - MRI difficulties, i.e. movement, etc. I would only assume 70% from the other sites - but that is just a guess. And I am in a negative mood today anyway.
>
> susan
>
> Ok - 9 sites, how many patients do you think they could get from the primary study - I can assume 100% of the survivors from Stanford and Houston.
>
> Thanks
> Rose

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wednesday, December 29, 2004 12:36 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT MRI Secondary

Rose,

I hate to be negative, but I think it would be more reasonable to say that 9 sites are likely to participate. Here's my reasoning:

Among the sites that said "yes" or didn't answer

Case - I am not sure about

Wayne - I think WOULD participate

Miami - thier MRI requires transport to another facility, and I think they would NOT be able to reasonbly participate

CinA - MRI requires transport

CinB - I think they WOULD participate

Indiana - I think they WOULD

Yale - question here - their MRI is some distance away

Brown - I have talked to Betty previously and she doesn't think they would be able to participate because of the MRI distance

Stanford - yes

UAB - yes

Houston - yes

Duke - yes

Wake Forest - I think yes

Rochesteer - not sure

UCSD1 - MRI requires ambulance or transport - so maybe NOT

UCSD2 - yes

So, that leaves 9 sites that I would be MORE sure about.

Thanks

Susan

Susan

Thanks for getting back to me - do you think it would be reasonable to

estimate that 11 sites would participate and we could potentially get half of the kids enrolled in SUPPORT at each site? (There will be site variation - e.g. Stanford and Houston will get close to 100% of survivors).

Thanks

Rose

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wednesday, December 29, 2004 12:11 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT MRI Secondary

Hi Rose,

Attached is the most recently updated survey (updated in November). Look at question 10 - this is the question that queries whether a site would be interested in participating.

By the way, I forgot that I had added question 8 - it is a query about whether the site routinely performs near-term US for infants <28 weeks. I think I added that question when it looked like the MRI protocol would potentially be a secondary to SUPPORT.

Thanks

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Can you send me a list of the centers that said they would participate?
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From: Susan Hintz [mailto:srhintz@stanford.edu]
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I think it would be unreasonable to ask or expect all the centers to participate in the secondary. Given the responses from the questionnaire, it's pretty clear that several centers don't even have an MRI in the same building and that an AMBULANCE transport would be required! Only 9 centers even said they would be interested in participating in the MRI portion of the study.

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I am working on this budget - I have a few questions -

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Do you think that all of the sites would get a head US either between day 7-14 OR prior to discharge as part of standard practice (at least one)?

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and one no vote. Therefore, I will send an email to the steering committee letting them know that this is going for outside review.

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Have a wonderful holiday

Thanks for all your effort!!
Rose

Rosemary D. Higgins, M.D.

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Pregnancy and Perinatology Branch

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From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT MRI Secondary
Date: Wednesday, December 29, 2004 12:04:52 PM
Attachments: Survey_Results1.xls

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	Case	Dallas	Wayne	Miami	Emory	CinA	CinB	CinC	Indiana	Yale	Brown	Stanford	UAB	Houston	Duke	WF	Roch	UCSD1	UCSD2
1. Does your site currently obtain cranial ultrasound at 7-14 days of age for infants<28 weeks EGA?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No(earlier)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Does your site currently obtain brain MRI in preterm or VLBW infants as the routine near-term neuroimaging study?	No	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes	No	No	No	No	No
If Yes, what is your estimated success rate in obtaining MRI among <28 weeks EGA?												90%		90%	3%			10%	
If No, does your site plan to implement brain MRI as the routine near-term neuroimaging study in preterm or VLBW?	No	No	No	Not Sure	No	No	Not Sure	No	No	Not sure	No		No		No	Not sure	No	Yes	No
a. Does your site obtain MRIs among preterm/VLBW infants on a case-by-case basis (severe US abnormalities, seizures, etc)?	Yes	Yes	Yes	Yes	Yes	Yes at Children's	Yes	No	Yes	Yes	Yes		Yes		Yes	Yes	Yes rarely done	Yes	Yes
3. Does your site use sedation for all of some brain MRIs? All/Some If some, percentage:	80-90%	Some	All	All	All	All	Some 99%	N/A	All	Some (<10%)	All	Some 20%	All	Some 50%	All	All	some 25-50%		All
4. When using MR facilities for <28 week near-term studies, does your site use the MR during "clinical magnet time or "research" magnet time	Clinical	Clinical	N/A Do not do them	Clinical	Clinical	N/A do not do them	Clinical		No difference at our site	Cinical and Research	No difference at our site	No difference at our site	Clinical	Clinical No difference	No difference	Clinical	No difference	Clinical	No differenc e
5. Is your MR in the same building as your NICU? If No, indicate where it is located.	No Adjacent Bldg	No Children's Med. Cen	No Accessible via tunnel	No diff. bldg	No between main Hosp &Children's	No at Children's	Yes	No at Children's	No	blocks from NICU	No Adjoining hospital	Yes	Yes	Yes	Yes	No	Yes	No Across street	No San Diego Child
a. Does your MR require a transport process including an ambulance?	No	No	No	Yes/No better eqp off	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	Yes	No
6. What type (i.e., GE, Siemens,etc) and magnet size (i.e. 1.5T) is used at your site?	Siemens 1.5T	There are 2-3	GE Signa Horizon LX 1.5T	Phillips 1.5T	Siemen Symphony 1.5T		GE 1.5T and Siemens 3T		2 GE's 1.5	Siemens 1.5T	Siemens 1.5T	GE 1.5T	GE 1.5	GE & Phillips 1.5T	GE Signa,Siemens Smyphony,Trio 1.5T 3T 3T	GE	GE 1.5T	GE 1.5 Tesia	GE 1.5T
7.Is diffusion tensor imaging performed at your site, or do you anticipate this capability in the near future?	No	Yes	Yes		Not Sure		Yes	No	Not sure	Yes	Yes	Yes	Yes	Not sure	Yes	Yes	Yes	Yes	Yes
8. Does your site routinely obtain cranial US prior to discharge (near-term 35-42 weeks PMA) for infants <28 weeks EGA?	Yes	Yes	Yes	Yes	Yes	Yes		No	No	Yes	No	No - MRI	No	No - MRI	No	Yes	No	Yes	Yes
9. Please indicate the NIH-negotiated rate for the following studies at your site:	Brain: 1500 Cranial US 225	No Brain MRI: 1235-2650? Cranial: 160-300	Brain:$775 Cranial: Not charge (SOC)		Brain:N/A Cranial US: N/A		Brain: 1138 Cranial US 960	Cranial US 375	Checking on this	$1551 w/0 contrast $1634 w/ contrast	Brain: 1046 Cranial US 198	Brain: 906.60 Cranial US 210.29	617.04 Cranial US 216.50	Will Check	Brain: 450/hr Cranial US 240		Brain: 533Cranial US 162	Brain: 500/hr Cranial 120	Brain Unk: Cranial US 365
10. Even if your site does not routinely perform brain MRI as the near-term neuroimaging study, would your site be interested in participating in a prospective study of near-term brain MRI and early and late cranial US among infants participating in the SUPPORT Study?		Not sure	Yes	Yes	No	Yes	Yes	Not Sure	Yes	Yes		Yes	Yes	Yes	Yes		Yes/Not sure	Yes	Yes

	Case	Dallas	Wayne	Miami	Emory	CinA	CinB	CinC	Indiana	Yale	Brown	Stanford	UAB	Houston	Duke	WF	Roch	UCSD1	UCSD2
11. Are there other limiting factors to obtaining brain MRIs in <28 weeks EGA infants at near-term at your site?		Yes	Yes	No	No		No	Yes	Yes	No			No	No	Yes Coordinating time/cost		No	Yes	No

From: Higgins, Rosemary (NIH/NICHD)
To: AGL Whitelaw, Prof of Neonatal Medicine, Child Health, University of Bristol
Subject: RE: NICHD Neonatal Research Network Protocol Review Request
Date: Monday, December 27, 2004 9:30:00 AM
Attachments: whitelaw 12.27.04.doc
SC -SUPPORT.Hintz.secondary.rev.doc
Support protocol.pdf

Dr. Whitelaw,
Thanks for getting back to me so quickly. I have attached the protocol, instructions and the primary SUPPORT protocol for reference. Let me know if you have any questions.
Thanks in advance for your help!
Rose

-----Original Message-----
From: AGL Whitelaw, Prof of Neonatal Medicine, Child Health, University of Bristol
[mailto:Andrew.Whitelaw@bristol.ac.uk]
Sent: Friday, December 24, 2004 6:20 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: NICHD Neonatal Research Network Protocol Review Request

Dear Rosemary,
I would be happy to review this research proposal by Jan 24 2005.
Andrew Whitelaw

--On 23 December 2004 13:54 -0500 "Higgins, Rosemary (NIH/NICHD)"
<higginsr@mail.nih.gov> wrote:

>
>
>
> HI,
>
> The Neonatal Research Network Steering Committee has recently approved a
> project titled
>
>
> Neuroimaging and neurodevelopmental outcome: A secondary to SURFACTANT
> POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL (SUPPORT)
>
>
>
>
>
> This is a secondary study to a previously approved SUPPORT Trial. I am
> wondering if you could confidentially review this protocol by January 24,
> 2005. If so, please let me know and I can send it to you with the
> primary SUPPORT protocol and instructions for review.
>
>
>
> Thanks
>
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> Rosemary D. Higgins, M.D.
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of Child Health
and Human Development
Bethesda, Maryland 20892
6100 Executive Boulevard
Room 4B03
Rockville, MD 20852

DATE: December 27, 2004

TO: Dr. Andrew Whitelaw

FROM: Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPMRMC, NICHD, NIH

RE: Review of the protocol: Neuroimaging and neurodevelopmental outcome: A secondary to SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL (SUPPORT)

Enclosed you will find a copy of the protocol titled "Neuroimaging and neurodevelopmental outcome: A secondary to SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL (SUPPORT)" which the Neonatal Research Network's Steering Committee has approved. I have asked you, as one of a group of investigators with special expertise, to review the protocol for the Network. Please consider the following questions for comment in your review, which will be anonymous upon request.

1. Is the question significant? Is the question still unresolved?

2. What are the strengths and weaknesses of the following design elements:
   a. Primary and secondary outcome measures
   b. Eligibility, inclusion and exclusion criteria
   c. Study groups
   d. Assignment
   e. Masking
   f. Surveillance for complications
   g. Follow-up

3. Are there other important ancillary protocols (to be done at individual centers)? Should any ancillary project be a part of the primary study?

4. Do you anticipate any other problems with the trial?

Please feel free to comment on any other issues you feel are relevant.

Thank you for agreeing to review this protocol. The addition of external review to the process of protocol development of our trials has been invaluable.

Please email or fax your written response to me at higginsr@mail.nih.gov or (301) 496-3790 by January 30, 2005. Feel free to call me with any questions at (301) 435 - 7909

Susan Hintz, Stanford University

NEUROIMAGING AND NEURODEVELOPMENTAL OUTCOME: A SECONDARY TO SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL (SUPPORT)

A. Abstract/Statement of Problem

Cranial ultrasound (US) is currently used for brain imaging in the extremely preterm population, but this modality cannot detect subtle brain injury that may be responsible for later neuromotor and cognitive delay. Magnetic resonance imaging (MRI) can identify brain structural abnormalities and white matter injury better than cranial US. The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) will evaluate if permissive ventilation strategies and lower SpO_2 targets will result in increased rates of survival without bronchopulmonary dysplasia (BPD) and increased rates of survival without retinopathy of prematurity (ROP) among 24-27+6/7 week EGA infants. It is not known whether differing ventilation and oxygenation management approaches could lead to adverse consequences with respect to brain injury. Extremely premature infants are at very high risk for neuromotor and neurodevelopmental impairment, with reported rates of cerebral palsy (CP) ranging from 11-20%, and of severe cognitive delay ranging from 30-60%. Whether MRI and predict neurodevelopmental outcome better than early and/or late cranial US among preterm infants is not yet known, but small preliminary studies are promising. We therefore propose a secondary study to SUPPORT in which specifically timed cranial US (for SUPPORT subjects in all Network centers) and brain MRI (in Network centers able to participate in the brain MRI portion of this proposal) will be obtained. We will use neurodevelopmental follow-up data at 18-22 months corrected age to assess comparative and combined predictive capabilities of these neurodiagnostic modalities ("early" cranial US, "late" cranial US and MRI). We will also test the hypothesis that ventilation and oxygenation strategies in SUPPORT will not be associated with an increase in death or brain injury (Grade 3/4 IVH by cranial US at 7-14 days or 35-42 weeks, abnormal brain MRI at 35-42 weeks). The NICHD Neonatal Research Network is uniquely positioned to embark upon such a project, which would be the first multicenter, prospective study to investigate these important questions.

B. Objective

We propose a secondary, prospective study of cranial US at 7-14 days ("early") and 35-42 weeks postmenstrual age (PMA) ("late") (for SUPPORT subjects in all Network centers), and brain MRI at 35-42 weeks PMA (in centers able to participate in the brain MRI portion of this proposal) among infants enrolled in SUPPORT. We propose to evaluate and compare the capabilities of early and late cranial US and brain MRI to predict neuromotor and neurodevelopmental outcome at 18-22 months corrected age through development of predictive models.

We also propose to determine if ventilatory or oxygen saturation interventions are associated with differences in the outcomes of death or abnormal neuroimaging findings (death/grade 3/4 IVH on "early" US, death/grade 3/4 IVH on "late" US, death/PVL, death/abnormal MRI).

C. Hypotheses

- Multivariate modeling will demonstrate that conventional brain MRI at 35-42 weeks PMA will be superior to cranial US in predicting neurodevelopmental outcome at 18-22 months corrected age.
- There will be insufficient evidence to reject the null hypothesis that no differences exist in frequency of Death/Grade 3/4 IVH or Death/PVL on early or late US between Low and High SpO_2 groups, or between Early CPAP and Control ventilation groups
- There will be insufficient evidence to reject the null hypothesis that the frequency of Death/abnormal findings on conventional brain MRI at 35-42 weeks postmenstrual age (PMA) are not different between Low and High SpO2 groups, or between Early CPAP and Control ventilation groups.

D. Specific Aims

1) To obtain consistently performed, timed and interpreted neuroimaging studies in extremely preterm infants enrolled in SUPPORT:
    a. cranial US at 7-14 days of age (in all centers)
    b. cranial US at 35-42 weeks PMA (in all centers)
    c. MRI at 35-42 weeks PMA (in centers participating in MRI portion of this secondary)
2) To compare early and late US and MRI findings between Low and High SpO_2 groups, and between Early CPAP and Control ventilation groups.
3) To utilize the NICHD Neonatal Research Network follow-up programs to assess neurodevelopmental outcomes at 18-22 months corrected age, as described in SUPPORT.
4) To examine the independent associations of neuroimaging findings with neurodevelopmental outcomes through logistic regression modeling.
    a. Regression models will assess the absolute and relative value of early and late cranial US, and brain MRI, alone and in combination with traditional risk factors, to predict both abnormal and normal neurodevelopmental outcome at 18-22 months.
    b. Through stepwise regression modeling, we will also assess the value of neuroimaging findings, alone and in combination, in predicting neurodevelopmental outcomes over and above the value of early risk factors or early and in-hospital risk factors alone.

E. Background, Significance and Rationale

The importance of an advanced neuroimaging component to SUPPORT:

SUPPORT will be the largest randomized controlled trial of ventilatory and oxygen saturation target management in extremely premature infants to date. Although the primary outcomes for the SUPPORT focus on survival without BPD and survival without ROP, it will be crucial to evaluate the potential impact of study interventions on both neuroimaging findings and neurodevelopmental outcomes. One possible concern could be that lower oxygenation parameters and less aggressive ventilatory management may be associated with a higher incidence of brain injury. This position might be extrapolated from earlier observations in preterm infants (1,2), and from studies of near-term and term hypoxic brain injury.

Other investigations suggest that more aggressive ventilation strategies leading to hypocapnia may place the premature infant at higher risk for reduced cerebral blood flow (CBF) and subsequent white matter injury. The CBF-carbon dioxide reactivity observed in adult animals may be blunted or incomplete in newborn and preterm animals (3,4). Nevertheless, several clinical case series of preterm infants have demonstrated strong associations of hypocapnia with significant abnormal findings on brain imaging and with adverse neurodevelopmental outcome (5-8), although other important risk factors were also identified.

At the very least, neuroimaging abnormalities in preterm infants are likely to be the result of a multifactorial process. Emerging evidence points to the unique vulnerability of the preterm infant brain in several respects. Low blood flow to the cerebral white matter and impaired cerebrovascular autoregulation in premature infants (9-11) may make subtle brain ischemic injury more likely. Coupled with this tendency to ischemic injury, is the vulnerability of developing oligodendroglial cells to damage (see below). Finally, it is possible that effects of exposure to *in utero* infection, frequently suspected in extremely preterm infants, may potentiate brain cellular injury caused by mild to moderate ischemia (12,13).

Summary: Given the interventions to be undertaken in SUPPORT, and the complexity and multifactorial nature of the development of white matter injury in the premature brain, advanced neuroimaging could be a critical component to the trial. This proposed secondary to SUPPORT would provide important additional information to investigators with respect to the impact of respiratory management on subtle brain injury.

The need to investigate emerging brain imaging modalities:

Premature infants are at high risk for neuromotor and neurodevelopmental impairment. Recent reported rates of cerebral palsy (CP) at 18-24 months corrected age range from 11-20%, and of cognitive delay range from 30-60% for the extremely low birth weight (ELBW) population (14-16). Yet, despite numerous investigations, the complete explanation of these impairments remains unclear. Correlation of specific neonatal factors, particularly neuroimaging findings, with adverse neuromotor and neurodevelopmental outcomes are frequently demonstrated. Many studies have emphasized the association of cranial US abnormalities including intraventricular hemorrhage (IVH) grades 3 and 4, periventricular leukomalacia (PVL) and ventricular dilatation with subsequent neurologic and cognitive impairment (14-20). Most investigators have found abnormalities on cranial US to be an independent risk factor for neuromotor abnormalities, but not necessarily for cognitive impairment.

But, the finding of severe cranial US abnormalities is not uniformly predictive of adverse neuromotor outcome in the premature population. In a study of perinatal correlates of neurologic impairment at 18-22 months corrected age among VLBW infants (20), only 52% of the infants with CP on follow-up had had severe cranial US abnormalities. This finding was in contrast to a 12% rate of severe cranial US abnormalities among matched controls without CP. In a neurodevelopmental follow-up study of ELBW infants in a multicenter, double masked, randomized controlled trial of indomethacin prophylaxis in preterms (TIPP), rates of survival without neurosensory impairment were found to be similar between treatment groups although incidence of

grade 3 or 4 IVH on cranial US had been significantly reduced by treatment with indomethacin (21).

Smaller studies have investigated the capabilities of cranial US at term to predict CP among preterm infants, revealing that the sensitivity of this diagnostic tool is only approximately 60% (22,23). Other reports have indicated that cystic PVL may be detected in infants without previous cranial US abnormalities at several months of age (24-26). These studies suggest that only certain types of brain injury may be detectable with cranial US, and that timing of studies may be crucial. Furthermore, the radiologic changes associated with PVL may be visible by US only at a particular point in time; if cysts do not form as a result of injury leading to PVL, it may not be visible by US. Thus, injury could have occurred but would not be detected by US.

Summary: Cranial US, the imaging modality currently considered to be standard of care, may not be sensitive enough to detect brain injury that is responsible for later neuromotor or neurodevelopmental delay among ELBW infants.

MRI compared with cranial US to assess of brain injury and predict neurologic outcome

MRI provides a more complete and anatomically detailed evaluation of the neonatal brain. Several studies have compared the relative capabilities of US with MRI to detect brain injury among preterm infants in the newborn period. These reports concluded that MRI detects white matter injury better than HUS (27-29), and provides additional information regarding hemorrhage and cystic changes not noted by cranial US. Childs, et. al. assessed MRI and serial cranial US in both preterm and term infants, and concluded that MRI was more sensitive in identifying periventricular white matter lesions (30). However, neurodevelopmental outcome of the infants in those studies were not reported.

Few studies have compared MRI with cranial US in terms of their capabilities to predict neurodevelopmental outcome among premature infants; those are small, primarily single-center efforts. Furthermore, due to variability of timing, of imaging, and differences in MRI scoring and interpretation, the studies are difficult to compare. Valkama, et. al. (31) assessed MRI compared with cranial US performed at term in 51 VLBW, preterm infants (<34 weeks). Twelve infants were diagnosed with CP at 18 months corrected age. MRI parenchymal lesions predicted CP with 100% sensitivity and 79% specificity whereas US at term predicted CP with 67% sensitivity and 85% specificity. The authors concluded that MRI was the more reliable methodology. Stanford University researchers (see below "Preliminary Studies and Results") have completed a prospective study of neuroimaging among VLBW, preterm infants with neurodevelopmental follow-up at 18-22 months and 30 months corrected age (32). MRI at term predicted CP with superior sensitivity and positive predictive value compared with early cranial US.

Other studies have suggested the potential prognostic advantages of MRI compared with cranial US. Roelant-van Rijn and colleagues (33) studied 61 preterm infants with cranial US, and MRI within the first weeks of age and/or at term. MRI at term was found to be helpful in delineating internal capsule abnormalities, considered to be useful in predicting later hemiplegia. Other preliminary reports include that of Austin, et. al. (34) in which 93 VLBW infants evaluated with brain MRI at term underwent

neurodevelopmental assessments at one year corrected age. White matter injury on MRI at term was correlated with neuromotor abnormalities such as hypertonicity, hypotonicity, and motor delay. In a very small group of premature infants <36 weeks, Miller, et. al. (35) showed that cerebellar hemorrhages detected by MRI, even if not associated with white matter injury, appeared to be associated with adverse neurodevelopmental outcome at 12 months.

There are potential criticisms to these studies. In most cases, MRI was compared with only "late" cranial US or only "early" US; a more complete comparison would include both early and late cranial US, demonstrating that the design of neuroimaging collection strategies in prospective studies is crucial. Many studies focus narrowly on neuromotor outcome, specifically the prevalence of CP, as outcome variables. A broader neurodevelopmental assessment and comparison is warranted. Finally, all studies of MRI findings and correlation with neurodevelopmental outcomes in preterm infants thus far are small; it is therefore not possible to draw powerful conclusions, especially with regard to ELBW patients. In fact, the recently published "Practice Parameter: Neuroimaging of the Neonate" (36) failed to definitively recommend routine MRI for VLBW preterm infants in large part due to the lack of follow-up studies. But, many of the reports reviewed above were not available during the development of the "Practice Parameter".

Summary: Studies to date suggest that MRI may be a more powerful tool in predicting adverse neuromotor outcome among preterm infants. However, timing of studies vary between published reports, and very few prospective neurodevelopmental follow-up investigations have been undertaken to assess the comparative prognostic capabilities of these neuroimaging techniques for neuromotor and cognitive outcomes.

The importance of subtle white matter injury

Periventricular leukomalacia (PVL) has been categorized as "focal" and "diffuse" (37,38). Focal PVL has been described as the result of severe ischemic-necrotic injury and is located deep in the white matter. This type of injury may lead to the development of cystic changes or significant findings that can be detected by cranial US or conventional MRI. Diffuse PVL is thought to be the result of less severe injury, diffusely located in the white matter. The mechanism of diffuse PVL may be multifactorial, including: 1) mild to moderate ischemia due to decreases in cerebral blood flow consistent with impaired autoregulation, 2) vulnerability of immature oligodendroglial cells to ischemic injury and damage by chemical mediators, and 3) oligodendroglial cell susceptibility to injury and death after intraventricular hemorrhage due to creation of oxygen free radicals. The sensitivity of the immature oligodendroglial cells to cytokine-induced injury may help to provide a pathophysiologic explanation to the observations of increased CP rates among infants born to mothers with chorioamnionitis, and among infants with early sepsis.

Diffuse PVL may be a clinically important and prevalent white matter injury in the preterm infant. Yet, diffuse PVL is unlikely to be seen by cranial US. Diffuse PVL may also be challenging to detect reliably on conventional MRI. However, in a study by Counsell et. al. (39), diffuse excessive high signal intensity (DEHSI) in the white matter of preterm infants at near-term was associated with higher apparent diffusion coefficient

values on diffusion weighted MRI. This finding suggested that subtle injury, causing changes in cellular differentiation and probable preferential death of preoligodendrocytes, resulting in diffuse PVL (40), may be structurally visible in the form of DEHSI. The developmental significance for the preterm infant is not known. It is also important to note that not all subtle white matter injury is likely to be detectable even by MRI.

Summary: IVH and focal cystic PVL are detectable by conventional MRI or even cranial US. However, more subtle factors and injuries may lead to oligodendroglial cell death and diffuse PVL. Diffuse PVL is not likely to be detected by cranial US, but might be detected by MRI. Such injury may have a substantial impact on normal white matter development and neuromotor outcome in the preterm infant; however, this question has been poorly studied in a large-scale, prospective manner.

Preliminary Studies and Results

A coordinated effort among neonatologists, radiologists, engineers, technicians and developmentalists has been in place at Lucile Salter Packard Children's Hospital and the Lucas Center for Nuclear Magnetic Resonance at Stanford University since the late 1990's. The objective of this group has been to combine the talents and expertise from various fields of science to investigate novel, potentially clinically relevant neuroimaging approaches in term and preterm infants. As a result, a strong infrastructure exists to allow for the development and implementation of further prospective studies and trials of MRI in the neonatal population.

Cranial US vs. conventional MRI for prediction of CP in VLBW infants: Infants of <1250 grams and <30 weeks EGA were enrolled a prospective observational study of the capabilities of early cranial US compared with conventional MRI at near-term to predict CP at 18-22 months corrected age, and 30 months (32). Cranial US was obtained twice during the first two weeks of life, and the most abnormal findings were used for analysis. Conventional MRI and cranial US were scored with respect to size of hemorrhage, parenchymal involvement, and ventricular dilitation. 62 infants participated in the study, with one excluded from analysis due to a later diagnosis of muscular dystrophy. The sensitivity and specificity of near-term MRI for predicting CP at 18-22 months were 71% and 91% respectively. The sensitivity of MRI for predicting CP at 30 months of age increased to 86% with the specificity remaining high at 89%. Although the specificity was comparable to MRI, the sensitivity of US to predict CP was only 29% at 18-22 months and 43% at 30 months. The positive predictive value of US was 22% at 18-22 months and 33% at 30 months.

This study, one of the largest prospective comparative neuroimaging studies of VLBW infants and neurodevelopmental outcome, supports the suggestion that conventional MRI may be superior to cranial US with respect to prediction of neuromotor abnormalities. There are limitations to this study, however. Comparison cranial US were performed early in the hospital course (<2 weeks), and no US contemporaneous with the MRI were routinely obtained. Recent studies by other investigators have also determined that, among VLBW infants, early cranial US poorly predicts non-cystic white matter injury on MRI at term (41). Also, previous reports by

Valkama, et. al. (31) suggest that cranial US at term was a substantially less sensitive predictor of CP than MRI at term. Nevertheless, a thorough comparison would include early and later cranial US determinations to evaluate the potential combined prognostic power of early and late cranial US compared with MRI at term. In addition, this study was significantly limited by small sample size, with only seven infants diagnosed with CP on neurodevelopmental follow-up. Sample size considerations also restricted possibilities for multivariate modeling of outcomes, and meaningful analysis of Bayley Scales of Infant Development II scores. All of these limitations could be addressed in the proposed prospective multicenter study.

F. Research Design and Methods

1. Study Design: This proposed secondary to SUPPORT is a prospective study of traditional (cranial US at 7-14 days and 35-42 weeks PMA) and advanced (MRI at 35-42 weeks PMA) neuroimaging with respect to SUPPORT randomized ventilation and oxygen saturation interventions. The capabilities of these neuroimaging modalities to predict neurodevelopmental outcome at 18-22 months corrected age will also be assessed. **It is proposed that all subjects enrolled in SUPPORT should be able to participate in the cranial US portion of this proposal. It is understood that not all sites will be able to participate in the MRI portion of the proposed secondary. (SEE 3.b "Neuroimaging studies" below)**

Perinatal, demographic and neonatal data will be collected as part of the ongoing NICHD Neonatal Research Network Survey of Morbidity and Mortality Among VLBW Infants (401-1500g) for the purposes of the study. Cranial US will be obtained at 7-14 days and at 35-42 weeks PMA. *Clinical* interpretation of cranial US will continue to be performed at individual Network sites, but for purposes of research outcomes, cranial US should ideally be interpreted by central readers. Brain MRI will be obtained at 35-42 weeks PMA; MRI will be interpreted by a central reader(s) for purposes of research outcomes, but clinical interpretation will be performed at individual Network sites. Detailed neuromotor and neurodevelopmental examinations will be undertaken at 18-22 months corrected age as part of the NICHD Cooperative Multicenter Network of Neonatal Intensive Care Units: Follow-Up of ELBW Infants (401-1000g), and per SUPPORT protocol.

Statistical analysis will include bivariate analyses, and logistic regression modeling to 1) assess the association of SUPPORT ventilation and oxygenation randomized treatment groups with neuroimaging, 2) evaluate the strength of independent associations of specific neuroimaging findings with neurodevelopmental outcomes and 3) develop predictive models.

2. Study Population

Inclusion Criteria

- Enrolled in the NICHD Neonatal Research Network SUPPORT study
- **FOR ALL CENTERS:** Cranial ultrasound can be obtained at 7-14 days of age and at 35-42 weeks PMA
- **FOR CENTERS PARTICIPATING IN BRAIN MRI PORTION OF PROPOSED SECONDARY:** Brain MRI can be obtained per study specifications (see Appendix D) at 35-42 weeks PMA.

- If MRI cannot be performed by 42 weeks due to subject clinical condition (See Appendix B), the "late" cranial US would also be delayed such that the cranial US is within 7 days of the brain MRI.

Exclusion Criteria

- **FOR ALL CENTERS:** Patient is likely to be discharged or transferred by 35 weeks PMA to a facility where cranial US is NOT available.
- **FOR CENTERS PARTICIPATING IN BRAIN MRI PORTION OF PROPOSED SECONDARY:** Patient is likely to be discharged or transferred by 35 weeks PMA to a facility where cranial MRI is not available.
- Patient unlikely or family unwilling to participate in neurodevelopmental assessment at 18-22 month corrected age
- Presence of known or suspected congenital anomalies including:
  - ➤ Chromosomal anomalies
  - ➤ Complex congenital heart disease (PDA, small muscular VSD or PFO are NOT considered to be congenital heart disease for the purposes of this study)
  - ➤ Congenital infection (TORCH, untreated maternal HIV, syphilis)
- Lack of informed consent

Enrollment of Subjects

Screening: Each center will be responsible for devising a screening strategy to identify all potential participants using the study inclusion and exclusion criteria. Screening and identification of patients should take place by 14 days of age since the "early cranial US" must be performed at 7-14 days.

Informed consent: Each participating center will follow procedures for developing informed consents as set out by the local Institutional Review Board (IRB). It is expected that the parents of all eligible infants will be approached to participate in this prospective study, and informed consent must be obtained by the individual center.

Eligible infants not enrolled: The reasons for non-enrollment will be documented. Short- and long-term outcomes of eligible infants not enrolled in this study will be documented as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality in VLBW Infants (Generic Data Base (GDB)) and, if enrolled, as part of the ongoing NICHD Neonatal Research Network ELBW neurodevelopmental follow-up study.

No MRI obtained for infants enrolled in the MRI portion of the study: An important objective of the proposed study requires acquisition of MRI at 35-42 weeks PMA; it is important that each participating center make this a priority. However, it is understood that if the patient is deemed medically unstable (Appendix B) during the entire 35-42 week PMA period, an MRI will not be obtained during that period. If the patient is medical unstable, MRI MAY BE DELAYED beyond 42 weeks, however LATE CRANIAL US SHOULD ALSO BE DELAYED in that case, such that the studies are still obtained within 7 days of each other.

3. BASELINE DATA, NEUROIMAGING, NEURODEVELOPMENTAL FOLLOW-UP

a. Baseline Data: Perinatal, demographic and in-hospital variables

i. INTRODUCTION AND FEASIBILITY: This secondary protocol will not require substantial data collection in addition to that already in place at participating centers; nor

will it mandate patient management. The majority of data collection instruments will be those already in routine use in the participating centers through the NICHD Neonatal Research Network Survey of Morbidity and Mortality in VLBW Infants. These data are obtained through the use of "Generic Data Base forms" which allows for consistent accrual of demographic, perinatal and neonatal variables among this high-risk population.

ii. METHODS: Research nurses at participating centers will collect data using the standardized Generic Data Base Forms. Additional queries will attempt to delineate the potential independent contribution of hypotension and hypocarbia, purported to be causes of cerebral hypoperfusion (42-46) leading to diffuse or focal neonatal brain injury, to abnormalities on MRI. These questions will be coordinated with the SUPPORT protocol subcommittee and focus on 1) need for pressors and 2) the degree of hypocarbia experienced

Since these infants will be participating in the SUPPORT trial, information regarding ventilation strategy and oxygen saturation randomization arms will also be available.

b) Neuroimaging studies

i. INTRODUCTION AND FEASIBILITY: Changes in the approach to neuroimaging may be required for implementation of this research protocol at participating centers. The extent of the changes will depend upon the procedures already in place at each individual center, and the level of participation (i.e., cranial US portion ONLY vs. cranial US and brain MRI portions of this secondary). In addition, budgetary constraints may limit participation.

CRANIAL US: Within the Neonatal Research Network, cranial US should already routinely be performed in ELBW infants 7-14 days of age window, and should also be performed at near-term among sites that are not performing MRI as the near-term brain imaging modality. The most recent results (November 2004) of the Preterm Infant Neuroimaging Questionnaire indicate that all but one Network center reported that cranial US are routinely obtained at 7-14 days among infants <28 weeks EGA. The one remaining center reported obtaining cranial US earlier than 7 days. Therefore, for the cranial US portion of this proposed secondary, **no additional imaging would be required for sites using only US as the routine neuroimaging modality.** For the purposes of this study however, central neuroimaging readers should ideally be used for both early and late cranial US since disparate interpretations of would potentially complicate analysis. Additional costs would therefore be incurred with respect to coordinator time (tracking, gathering, sending studies) and central reading.

BRAIN MRI: The most recent results (November 2004) of the Preterm Infant Neuroimaging Questionnaire reveal that two Network sites currently use brain MRI as the routine near-term VLBW imaging modality, with one additional site planning to implement routine MRI, and 4 other sites "considering" a change to MRI. Therefore, for those sites utilizing MRI as the routine near-term neuroimaging modality, **only one additional study, a cranial US at near-term, would be required.** In addition to the cost of the additional imaging study, costs would be incurred as noted above with respect to coordinator time and central reading.

WHICH CENTERS WILL PARTICIPATE IN THE BRAIN MRI PORTION OF THIS PROPOSED SECONDARY? Network centers with devices capable of performing neonatal conventional brain MRI (4 mm slice) could participate in the MRI portion of this proposed study. **Sites not performing brain MRI as the routine near-term neuroimaging study MAY be able to participate in the Brain MRI portion of this secondary. However, due to budgetary considerations, it is possible that implementation of this proposed secondary may be limited only to selected Network sites.** The most conservative approach would be that only those sites in which MRI is currently, or will soon be, implementing routine near-term MRI will participate in this proposed secondary.

ii. METHODS:

1) "Early cranial ultrasound": A cranial ultrasound will be obtained at 7-14 days of age. If more than one cranial ultrasound is obtained during that time period, the ultrasound obtained closest to 14 days will be used. Results will be interpreted as indicated in the Manual of Operations (See Appendix C), and reported in the NG03 form, but central readers will formally interpret ultrasounds.

Although not currently *required* within the parameters of the NICHD Neonatal Network VLBW Registry, recent ELBW neurodevelopmental follow-up studies from the NICHD Neonatal Research Network reveal that virtually all of these extremely high risk infants surviving to the 18-22 month visit have had at least one cranial US early in the course of their hospitalization. Furthermore, the "Practice Parameter" for neuroimaging in the neonate recommends *screening cranial US should be performed on all infants with EGA of <30 weeks at 7-14 days of age* (36); it is likely that Network centers have already implemented this practice to patient care protocols.

2) "Late cranial ultrasound": A cranial ultrasound will be obtained at 35-42 weeks PMA, and within 7 days of brain MRI. All late cranial US will be reported in the NG03 form as indicated in the Manual of Operations (See Appendix C), and will be interpreted by central readers.

Late cranial US is not currently required in the Network paradigm. However, the "Practice Parameter" as referred to above (36) recommends that *cranial US should be optimally repeated at 36-40 weeks' postmenstrual age*, so it is likely that Network sites have implemented this routine imaging.

FOR CENTERS PARTICIPATING IN THE BRAIN MRI PORTION OF THE PROPOSED STUDY:

3) Brain MRI: A brain MRI will be obtained at 35-42 weeks PMA, and within 7 days of the "late cranial ultrasound". Images will be acquired as described in Appendix A. Conventional MRI images will be transferred to Stanford University for interpretation and scoring by central pediatric neuroradiologist reader(s) (Patrick Barnes, M.D., and others as suggested by the Steering Committee) who will be masked to any unique patient identifiers and to patient history and outcome. Dr. Barnes is a highly regarded, widely published pediatric neuroradiologist with extensive experience in the field of MRI, MR spectroscopy, diffusion weighted and diffusion tensor imaging. In addition to his dedicated work at Stanford University, Dr. Barnes has also collaborated with researchers such as TE Inder, PS Huppi and JJ Volpe. Dr. Barnes is an expert in the timing of fetal and neonatal brain injury using methods such as MRI and MRS.

MRI interpretation and data access: Conventional MRI images will be interpreted and scored by a central neuroradiology reader (Appendix C). The central reader(s) will be responsible for completion of data forms and data transfer to the Network Data Center. Each participating center is expected to counsel families with regard to MRI findings on the basis of its own neuroradiologist's interpretation of the images.

Sedation issues: MRI studies are performed without sedation at Stanford University. Patients are imaged following a feeding, ear plugs (MiniMuffs, Natus) are used to reduce the noise by up to 50% and patients are bundled to preserve warmth, maintain sleep and reduce patient motion. Of the 14 sites that responded to an earlier NICHD Neonatal Research Network Brain Imaging Survey (Dr. Seetha Shankaran), five indicated that they already use sedation for MRI. Another six sites indicated that sedation is used if clinically necessary. One site responded that sedation is not used. Responses from two centers were not clear. At Stanford, the approach of "feeding and swaddling" has yielded successful conventional MRI imaging with excellent quality in almost all cases. Sedation, if needed, would clearly increase the likelihood of obtaining a high quality scan. Network centers in which sedation is standard of care, and MRI is routinely performed, should certainly be able to continue their current approach. Although several of the sites have already indicated that sedation is used routinely, it is appreciated that the use of sedation in the context of a research protocol may make IRB approval more difficult. One possible solution for centers with such challenges would be to present two consent forms: the first for participation in the study itself, indicating that "feeding and swaddling" methods would be tried; the second, for consent to use sedation if this conservative approach were not successful, or if it is considered medically inadvisable to implement the "feeding and swaddling" approach (i.e., severe reflux). Clearly there are differing approaches to sedation for MRI studies, thus the issue of sedation will be left to the individual investigators at each Network site.

c) Neurodevelopmental Follow-up

i. INTRODUCTION AND FEASIBILITY: Neurodevelopmental follow-up for ELBW infants is already a focused objective within the NICHD Neonatal Research Network; all Network centers have complete neurodevelopmental assessment teams and patient tracking infrastructure in place. In addition, neurodevelopmental follow-up is already a part of SUPPORT protocol.

ii. METHODS: Follow-up visit will be conducted at 18-22 months corrected age as described in the "NICHD Neonatal Research Network ELBW Follow-Up Study Manual of Operations" (see Appendix C). An exam for neurological exam for cerebral palsy will be performed. The Bayley Scales of Infant Development (Bayley N. Bayley Scales of Infant Development-II. San Antonio, TX: Psychological Corporation; 1993) will be administered by a Bayley Examiner certified for the Follow-Up Study. In addition to neurodevelopmental assessments, information regarding socioeconomic status, level of education of the primary caregiver, and marital status is routinely obtained at the 18-22 month visit.

4. STATISTICAL CONSIDERATIONS

Outcomes:

Primary outcomes considered will include

- Death/Grade 3/4 IVH on 7-14 day cranial US
- Death/Grade 3/4 IVH on 35-42 week cranial US
- Death/PVL on 35-42 week cranial US
- Death/abnormal MRI at 35-42 weeks

Secondary outcomes will include
- cerebral palsy
- BSID MDI<70
- BSID PDI<70
- Neurodevelopmental impairment (NDI) defined as any of the following: deafness, blindness, moderate-severe cerebral palsy, or BSID II MDI or PDI score <70.

Bivariate analyses: Analyses of frequency of primary outcomes with respect to SUPPORT treatment groups will be undertaken. Comparisons will be made between ventilation strategy groups (Early CPAP and Control groups) within each randomized oxygenation group, and between oxygenation strategy groups (Low and High SpO2) within each randomized ventilation group. Continuous measures will be compared using the Student t-test and ANOVA where appropriate, and Chi-square analysis will be used to compare categorical data. These analyses would also adjust for the clustering effect introduced by randomizing by week of study.

Sample size and power issues:
Overall GDB and follow-up patient numbers: For year 2003, 1468 infants 24+0 to 27+6 weeks EGA were enrolled in GDB. Of those, 1249 survived to >7 days and 1209 survived to >=14 days. 1027 patients survived to hospital discharge. In year 2003, a total of 725 former 24+0 to 27+6 week EGA patients completed neurodevelopmental assessment at 18-22 months corrected age.
Frequency of neuroimaging outcomes:
Ultrasound: For year 2003, among infants 24+0 to 27+6 weeks EGA surviving to >=14 days, the frequency of Grade 3/4 IVH on cranial US was 20.3%; for those surviving to discharge it was 18.6%. The frequency of PVL among those surviving to discharge was 3.9%.
MRI: "Abnormal" conventional MRI results among preterm infants at near term are much more difficult to quantify. This is due both to a paucity of available data in the literature, and disparate methods of reporting and scoring "abnormalities" on brain MRI among preterm infants. Two recent studies have attempted to estimate the frequency of white matter signal abnormality, as well as other abnormal findings. Inder and colleagues (47) reported on findings of brain MRI performed at term equivalent age in 100 infants of 23-32 weeks EGA. Only 36/100 were considered to have no white matter signal abnormality, whereas 16/100 had extensive severe white matter signal abnormality. Cortical gray matter abnormalities were rare, with 96/100 patients categorized as normal. Lateral ventricle size was normal in only 40/100. Miller, et. al. (48) reported on MRI findings of 32 consecutive preterm infants, but imaging was performed at earlier postconceptual ages. In addition, previous studies by Maalouf (27) found that 12/19 (63%) preterm infants studied by MRI at 38-44 weeks PCA had abnormal white matter signal, but of those only 7 were moderately to severely abnormal (37%). Childs (30)

found 29 of 105 preterm infants (<37 weeks) had abnormal periventricular white matter on MRI, and an additional 5 infants with other abnormalities (32% abnormal). However, the age at the time of MRI in that study ranged from 1-42 days, and PCA at time of scan was not reported. Counsell, et. al. found that, among preterm infants at near term, 34 of 50 had "overt" white matter abnormality or diffuse excessive high signal intensity white matter abnormalities (68% abnormal) (39). In summary then, the frequency of "abnormal" brain MRI in preterm infants ranges from 32-68%. One projected benefit from this proposed secondary study, in fact, would be that the frequency of specific MRI abnormalities in a large premature group could be better clarified and described. For the purposes of sample size and power calculations for this proposal, a conservative estimate of 40% white matter abnormality by MRI at 35-42 weeks will be used.

Thus, the following are the estimated rates for four major outcomes examined in this proposal:

I) Death/Grade 3/4 IVH (14 day)	34.2%
II) Death/Grade 3/4 IVH (at d/c, an estimate of 35-42 weeks)	42.9%
III) Death/PVL (at d/c, an estimate of 35-42 weeks)	32.8%
IV) Death/MRI abnormality	58%

Sample size and detectable difference estimates if all centers could participate in both cranial US and brain MRI portions of study:
The revised projected sample size required for SUPPORT is 1310 patients (or 328 patients per each of 4 treatment groups). It is unlikely that all centers could participate in both cranial US and Brain MRI portions of this proposed study. But, if one used an estimate of 80% enrollment in the proposed study, 1048 patients would be enrolled. This would provide 262 patients in each for 4 groups, such that bivariate comparisons will be made between ventilation strategy groups (Early CPAP vs. Control ventilation groups) within each randomized oxygenation strategy, and between oxygenation strategy groups (Low vs. High SpO2) within each randomized ventilation strategy.

Note that 80% enrollment should be considered a conservative estimate for the cranial US portion of this study – virtually all SUPPORT subjects should be able to participate in the cranial US portion of this study.

Thus, for the outcome of Death/Grade 3/4 IVH (14 day), using an expected prevalence rate of 34.2% (see above), a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	33.9% = 34.2% to 22.6%
% increase from expected	35.9% = 34.2% to 46.4%

For the outcome of Death/Grade 3/4 IVH (35-42 week), using an expected prevalence rate of 42.9%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	28.4% = 42.9% to 30.7%

% increase from expected	29.4% = 42.9% to 55.4%

For the outcome of Death/PVL by cranial US (35-42 week), using an expected prevalence rate of 32.8%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	34.4% = 32.8% to 21.5%
% increase from expected	36.9% = 32.8% to 44.9%

As noted above, it is unlikely that 80% enrollment could be achieved for the Brain MRI portion of this study. However, if this were to be possible, the following would apply:

For the outcome of Death/MRI abnormality (35-42 week), using an expected prevalence rate of 58%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	21.6% = 58% to 45.5%
% increase from expected	20.7% = 58% to 70%

The detectable differences were also calculated for an alpha of 0.01 to adjust for the four primary outcomes. Thus,

For the outcome of Death/Grade 3/4 IVH (14 day), using an expected prevalence rate of 34.2% (see above), a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	40% = 34.2% to 20.5%
% increase from expected	43.2% = 34.2% to 49%

For the outcome of Death/Grade 3/4 IVH (35-42 week), using an expected prevalence rate of 42.9%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	33.6% = 42.9% to 28.5%
% increase from expected	35.2% = 42.9% to 58%

For the outcome of Death/PVL by cranial US (35-42 week), using an expected prevalence rate of 32.8%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	40.2% = 32.8% to 19.6%
% increase from expected	42.7% = 32.8% to 46.8%

For the outcome of Death/MRI abnormality (35-42 week), using an expected prevalence rate of 58%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	25.8% = 58% to 43%
% increase from expected	24.8% = 58% to 72.4%

If MRI could not be performed in all sites due to budgetary constraints, clearly differences between groups with respect to the outcome of Death/MRI abnormality would need to be larger in order to detect. If the number of patients involved in the MRI portion of the proposed study were reduced by one-half (to 524), then the sample size per group would drop to 131. In that case:

For the outcome of Death/MRI abnormality (35-42 weeks), using an expected prevalence rate of 58%, a projected sample size of 131 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	37% = 58% to 36.5%
% increase from expected	35.5% = 58% to 78.6%

However, recall that the estimate of 40% white matter abnormality on MRI among preterm infants at term is conservative, thus the estimate of 58% for the outcome of Death/MRI abnormality may also be conservative.

Regression Analyses: In addition to bivariate analyses, regression analyses will be undertaken to attempt to adjust for confounding variables in comparisons of treatment groups with respect to neuroimaging findings. The independent association of ventilation strategy will be determined for each neuroimaging outcome (Grade 3/4 IVH at 7-14 days, 35-42 weeks, PVL at 35-42 weeks, MRI abnormality), adjusting for gestational age, weight, and oxygenation strategy. Similarly, the independent association of oxygenation strategy will be determined for each neuroimaging outcome (Grade 3/4 IVH at 7-14 days, 35-42 weeks, PVL at 35-42 weeks, MRI abnormality), adjusting for gestational age, weight, and ventilation strategy.
Neurodevelopmental Outcomes Logistic Regression Models: We propose a novel approach to the comparison of neuroimaging modalities with respect to neurodevelopmental outcomes, that of logistic regression modeling. Numerous neurodevelopmental outcomes studies have used this approach, however previous studies of brain MRI in the premature infant have lacked the sample size to implement this statistical technique. Models will be developed to include perinatal, demographic, neonatal and socioeconomic factors pertinent to neurodevelopmental outcome as demonstrated in previous reports (14,15) and the univariate and multivariate analyses carried out. Neuroimaging study results (cranial US at 7-14 days, cranial US at 35-42 weeks PMA, and brain MRI at 35-42 weeks) will be added to the model individually and in combination, to determine the adjusted risk for adverse outcome that each imparts, and to ascertain if any two abnormal studies (i.e., early cranial US and MRI, or early and late US) are materially more predictive of neurodevelopmental impairment than any single abnormal study. Ventilatory strategy and oxygen saturation strategy will also be available as crucial neonatal factors that may impact on outcome.

Predictive modeling of outcome: Challenges to the development of a predictive model include the need for both a "model development" data set and a "model validation" data set. Possible solutions to this challenge include splitting the proposed study data set in half, thus creating a development and validation set; or by employing a so-called "boot-strapping" technique by which multiple random samples of the data set are used for calculating confidence intervals for predictions (49). Further analysis will be required to determine the best strategy for predictive modeling in the proposed study.

Further Statistical considerations: Development and comparison of predictive models:

I. Initial model development, the models and their variables.

The sample will be randomly split into a development dataset with 50% of cases and 50% of controls and a test dataset with 50% of cases and 50% of controls. Several models will be developed of which the following are projected to be central models; however, additional models may also be developed:

1. "Classic" risk model, including traditional factors (i.e., gestational age, birth weight, gender, race, maternal education, etc.) as well as "worst" early cranial US
2. Late cranial US model
3. Conventional MRI model

For each model, the number of categorical variables will be restricted to 5 – 10 observations per category cell. When candidate variables exceed this ratio, the best set of significant predictor variables will be chosen by forward selection. In this case, at each step the variable with the most significant effect will be identified and added to the model. The same dataset will be used for the development of each model.

II. Model calibration and goodness-of-fit

Each model will be calibrated using Pearson chi-square, likelihood ratio chi-square, and Hosmer and Lemeshow statistic.

III. Model discrimination and predictive ability

Sensitivity (true positive rate) and specificity (true negative rate) of the models to predict outcome will be evaluated. The receiver-operator curve (ROC) will be used to display model discrimination by plotting sensitivity against specificity. The predictive abilities of the models will be compared using area under the curve (AUC) analyses (Hanley JA and McNeil BJ, *Radiology* 1982)

IV. Multidimensional model.

Finally, we will attempt to build a model that combines the most significant factors from cranial US and MRI models and compare to the above models.

APPENDICES

Appendix A: Magnetic resonance imaging requirements and image acquisition

Conventional MRI: Network centers that have any "type" of device (i.e., GE, Philips, Siemens, etc.) capable of performing standardized conventional neonatal brain MRI

sequences with 4 mm contiguous slices (0mm gap) will be able to participate. All examinations will include conventional fast spin echo (FSE) T1-weighted and T2-weighted sequences as well as fluid attenuated inversion recovery (FLAIR) and gradient echo (GRE) sequences.

Appendix B: Medical instability at 35-42 week PMA MRI

For "medical instability" to be considered the cause of non-acquisition of MRI, one of the following conditions should exist during the entire 35-42 week PMA MRI imaging window:

- The patient is intubated.
- The patient is considered by the attending neonatologist to be critically unstable such that transport to the radiology suite would be unsafe.

Appendix C: Neuroimaging and neuromotor evaluation

Ultrasound scoring instruments will be modified from the PiNO central reader forms, but will include reference to the following findings, and will be delineated as unilateral or bilateral:

Early Cranial Ultrasound:

- Grade I: blood/echodensity in the germinal matrix/subependymal area
- Grade II: blood/echodensity in the lateral ventricle without distention
- Grade III: blood/echodensity in the lateral ventricle with distention
- Grade IV: blood/echodensity in the parenchyma
- Periventricular leukomalacia
- Cystic periventricular leukomalacia

Late Cranial Ultrasound

- See above
- Porencephalic cystic changes
- Ventriculomegaly
- Presence of shunt

Adjustments and amendments to the following MRI interpretation scheme may be made after further discussion and input from members of the Steering Committee and SUPPORT Subcommittee.

Conventional MRI interpretation:

- C1 = normal
- C2 = minimal subependymal hemorrhage or mineralization with no or mild ventriculomegaly
- C3 = moderate to severe ventriculomegaly
- C4 = parenchymal abnormality
- C5 = periventricular cystic abnormality
- C6 = white matter signal abnormality
- C7 = increased extra-axial fluid
- C8 = cerebellar hemorrhage or mineralization
- C9 = diffuse excessive high intensity signal

Cerebral Palsy ("Neonatal Research Network Follow-Up Study Manual of Operations")
Cerebral palsy at 18-22 months will be diagnosed if definite findings are encountered on exam in any two of the following three areas:

1) Delay in motor milestones – determined using the motor quotient as described in the Manual of Operations.
2) Abnormalities observed in the classical neuromotor exam, which includes measurement of tone, deep tendon reflexes, coordination and movement (not including eye movement). Any one abnormality, except for isolated low tone or toe walking is sufficient.
3) Aberrations in primitive reflexes and postural reactions – any aberration is sufficient.

Cerebral palsy will be further categorized by type and severity, as described in the Manual of Operations.

Human Subjects

1. Risks to the subjects:

a) Human Subjects Involvement and Characteristics: Infants enrolled in the NICHD Neonatal Research Network SUPPORT trial will be recruited. Inclusion and Exclusion criteria have been defined as stated in the Research Plan. The final population will be dependent upon the number of sites within the Network that participate in this study. Both male and female infants will be enrolled. We expect the study population to be representative of the racial background and gender distribution of the Neonatal Research Network. In 2001, 49% male and 51% female patients constituted the ELBW population of the Neonatal Research Network, of which 43% were black, 38% were white, 15% were hispanic, and 3% were other races.

b) Sources of Materials: Sources of research material will consist of perinatal, demographic and neonatal data collected by research personnel as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality Among VLBW Infants (401-1500 g), and through the data collection mechanisms associated with the SUPPORT trial. Additional data will be obtained through evaluation of brain MRI images by a central reader masked to all patient identifiers and patient outcomes. Data forms will be created, completed by the central MRI reader, and submitted to Research Triangle Institute per protocol. Neurodevelopmental outcome data will be obtained from the NICHD Neonatal Research Network Follow-up Study of ELBW Infants, and per SUPPORT specifications.

c) Potential Risks: The risks and discomforts of participation are minimal as the study relies primarily on data collected for ongoing studies already in progress, and uses non-invasive techniques. Cranial US is performed routinely in all NICU's in the NICHD Neonatal Research Network, is considered standard of care, and techniques would not be altered by this study. Brain MRI at 35-42 weeks postmenstrual age is already routine in several Network centers. Sedation will not be used routinely, although may be used particularly in centers that already do use sedation. Temporary minor skin irritation from tape used to apply MRI-compatible monitoring electrodes may occur, but this risk is unlikely. Temporary transport of a patient to a radiology suite for MRI may also represent a possible risk; however, only those patients considered stable for transport will undergo imaging, and a 7- week window of opportunity for MRI is built into

the proposed study. The alternative to obtaining a brain MRI as part of the proposed study is non-enrollment.

2. Adequacy of Protection Against Risks:
a) Recruitment and Informed Consent :
Screening: The individual center will be responsible for devising a screening strategy to identify all potential participants using the study inclusion and exclusion criteria. Screening, identification and informed consent procedures should be completed by 14 days of age as "early cranial US" must be performed by this time.
Informed consent: Each participating center will follow procedures for developing informed consents as set out by their Institutional Review Board (IRB). The parents of all infants enrolled in SUPPORT will be approached to participate in this secondary study, and informed consent must be obtained by the individual center. Informed consent will be obtained by the Principal Investigator or his/her designee.
Eligible infants not enrolled: The reasons for non-enrollment of eligible infants will be documented. Short- and long-term outcomes of eligible infants not enrolled in this study will be documented as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality in Very Low Birth Weight (VLBW) Infants (Generic Data Base (GDB)) and, if enrolled, as part of the ongoing NICHD Neonatal Research Network ELBW Neurodevelopmental Follow-Up Study.
No MRI obtained for enrolled infants: The objective of the proposed study requires acquisition of cranial US and MRI at 35-42 weeks PMA; if the patient is deemed medically unstable during the entire 35-42 week PMA period, an MRI will not be obtained. Other reasons for inability to obtain the MRI will also be documented.
b) Protection against risk: Every effort will be made to protect study patients from potential risks of participation. Stability of study patients for transport to a radiology suite for brain MRI will be assessed by the attending neonatologist at each participating site. Should a patient be judged to be unstable for transport to the radiology suite, a 7-week window of opportunity for MRI (35-42 weeks postmenstrual age) has been provided in the protocol. Any adverse events with regard to obtaining neuroimaging studies among enrolled patients will be documented and submitted to NICHD, the data center, and the local IRB. The NICHD Neonatal Research Network has an independent Data Safety Monitoring Committee (DSMC), which would provide continuous oversight of patient safety and risk factors for the duration of the study. The DSMC will review the study on at least an annual basis.

3. Potential Benefits of the proposed research to the subjects and others: The potential benefits of participation to an individual patient include identification of structural anomalies by MRI that would not have been identifiable by ultrasound. This may allow for early, targeted intervention for the individual patient that otherwise would not have been undertaken. Other potential benefits would be to future extremely preterm patients after results of this prospective study are known (see below).

4. Importance of the knowledge to be gained:
Provide a thorough neuroimaging monitoring arm for SUPPORT: Although cranial US is a standard diagnostic procedure in the NRN, the proposed study would provide a

framework for specifically timed cranial US studies, which would be more appropriately comparable. In addition, subtle but arguably extremely important findings consistent with brain injury would be detectable by MRI.
Counseling, follow-up: Detection of an injury pattern which is consistent with later neurodevelopmental delay will be useful for counseling and targeted, early follow-up. Identifying such a tool would provide a link to later research in early intervention.
Clarify the pathogenesis of injury leading to neurodevelopmental impairment: Further delineation of pathophysiologic correlates of later outcome could possibly be linked with perinatal and neonatal factors, which would 1) focus future research and intervention on clinical events associated with the pathophysiologic hallmark, 2) provide important data leading to further study of the pathogenesis and timing of injury, and 3) assess neuroanatomic localization of subtle injury associated with later neuromotor abnormalities.
Contribution to the literature with respect to diagnostic strategies for the extremely preterm population: Previous neuroimaging practice parameters have concluded that insufficient evidence exists to recommend advanced neuroimaging for premature infants for prediction of neurodevelopmental outcomes. The proposed study would address this significant gap in the collective literature.

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Protocol for the NICHD Neonatal Research Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial

Final

August 28, 2004
Revised September 16, 2004

1.1 Statement of Problem

At the present time, there is no recommendation or standard teaching regarding the early use of CPAP/PEEP during resuscitation and continuing after NICU admission for the extremely low birth weight (ELBW) infant. However, a number of studies, mostly retrospective in nature, have suggested that the use of early CPAP may be associated with improved outcomes, including a decreased need for mechanical ventilation, a decreased need for surfactant therapy, and a decrease in oxygen supplementation and/or death at 28 days after birth and at 36 weeks post menstrual age. There has not been a prospective study which has randomized ELBW infants to CPAP/PEEP beginning in the delivery room, and continuing in the NICU and a permissive ventilation strategy if intubation is required and compared their outcomes to infants treated with prophylactic or early natural surfactant, interventions with known efficacy in reducing mortality, severity of disease and the incidence of chronic lung disease (CLD).

Retinopathy of prematurity (ROP) remains a significant cause of morbidity among ELBW infants and its occurrence is inversely proportional to gestational age and duration of oxygen exposure. It is known that ROP is increased by the prolonged use of supplemental oxygen from observations published in the 1950s, and but early trials were unable to pinpoint the actual level of arterial PaO_2 which was the threshold for triggering the pathophysiology of this disorder.[1] However, there have been a very few prospective studies evaluating the benefit of higher versus lower levels of oxygenation in infants, especially for ELBW infants, none of which were performed during the acute illness. While retrospective cohort studies have suggested that the use of lower SpO2 ranges and adherence to strict nursery policies may result in a lower incidence of severe ROP, there is no current agreement on the accepted SpO2 ranges for managing the ELBW infant from birth.

1.2 Background

Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC). Although no formal recommendation has been made to date about maintaining PEEP in the delivery room setting, continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[2]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9hours ($\pm$12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[3] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[4]. Premature infants who do not achieve a FRC are more likely to develop hyaline membrane disease (HMD) requiring mechanical ventilation[5]. CPAP may prevent the excessive consumption of surfactant in newborn infants with limited surfactant production.[6] A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era suggested that early CPAP may improve survival in infants greater than 1500 gm.[7]

Similarly, there is no definite recommendation or standard teaching regarding the level of oxygenation that should be maintained in ELBW infants. Oxygen supplementation has to be used liberally as ELBW infants frequently have desaturation episodes and thus wide saturation ranges are tolerated clinically. However, oxygen toxicity can result in increased risk for CLD, retinopathy of prematurity (ROP) and other disorders. Alternatively, oxygen restriction may impair neurodevelopment. The pulse oximeter is a newer technology that can be used to improve the control of oxygenation levels. There is great potential benefit to determining the oxygenation levels that prevents ROP and CLD but does not result in neurodevelopmental impairment with a randomized controlled trial of levels of oxygen saturations on the high and low side of the currently utilized levels.

While prevention of hyperoxia may decrease the risk for ROP and CLD, efforts to maintain lower oxygenation levels may result in an increase in periods of hypoxemia because of the marked variability in oxygen in ELBW infants. Thus, it is necessary to determine if lower oxygenation levels that may prevent ROP and CLD are deleterious for brain development and result in impaired neurologic outcome.

1.3 Animal Studies

Nilsson et al demonstrated that the use of 5 cm H_2O PEEP in the initial ventilation of premature rabbit pups resulted in increased lung-thorax compliance, and reduced the extent of bronchiolar epithelial lesions seen with mechanical ventilation [8]. The use of early PEEP starting at delivery, improves the response to surfactant, improves lung mechanics increases surfactant pools, and reduces lung injury. [9,10]

More recently studies by Jobe et al have demonstrated that premature lambs treated with CPAP alone at birth had significantly decreased neutrophils and hydrogen peroxide in their alveolar wash when compared with animals who were ventilated from birth. [11]

1.4 Human Experience: Ventilatory Support

CPAP was introduced by Gregory et al in 1970 and was shown to improve gas exchange and outcomes in preterm infants with respiratory distress.[12] A subsequent review of CPAP for respiratory distress concluded that "In preterm infants with RDS the application of CDP either as CPAP or CNP is associated with benefits in terms of reduced respiratory failure and reduced mortality. CDP is associated with an increased rate of pneumothorax. The applicability of these results to current practice is difficult to assess, given the intensive care setting of the 1970s when four out of five of these trials were done." [13]

There is now a body of information from Europe that provides further evidence that early CPAP can reduce the need for intubation in a significant number of VLBW infants. Jonsson et al treated VLBW infants from 1988 to 1993 that required > 30% oxygen with nasal CPAP usually within 30 minutes of delivery[14]. From 1991 onward, infants with severe distress or apnea were intubated for a $PaCO_2$ greater than 60 mmHg, and were given surfactant. Twenty-five percent of all infants required only supplemental oxygen and 24% of all infants were ventilated from birth. Fifty-one percent were treated with nasal CPAP, with one-third of these subsequently requiring ventilation. Almost all infants < 24 weeks required ventilation suggesting that this group may require a different approach. Gittermann et al reported that the use of early CPAP for infants < 1500gm (VLBW) significantly reduced the frequency of intubation, reduced mortality ($p=0.038$), and shortened the duration of intubation and length of stay[15]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[16] in a report of 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 reported that there was an increase in the proportion of patients not intubated and mechanically ventilated from 7% to 14% in infants <1000 g and from 28% to 44% in those $\geq$1000 g ($P < 0.02$ and <0.01, respectively). The decrease in intubation was not associated with a significant increase in adverse outcome such as death, intraventricular hemorrhage, periventricular leukomalacia, or BPD. The proportion of infants <1000 g that survived without BPD increased from 38% in 1992 to 48% in 1994; $p < .05$, and the proportion of infants =1000 g in whom BPD developed decreased from 14% to 9%; $p < .05$. None of these observations was from a prospective controlled trial, and in none was there a contemporaneous control group who did not receive early CPAP.

The first prospective trial comparing prophylactic CPAP, started at birth, with conventional management was that of Han et al. They compared the use of nasal CPAP given by nasopharyngeal tube with conventional management in 82 infants, 32 weeks gestational age at birth, and in this study it would appear that CPAP was begun in the DR, but may have been delayed for up to 2 hours.[17] No infants in this trial received surfactant, and no mothers were treated with antenatal steroid. There was no advantage observed with the use of early CPAP, and oxygenation was worse in the early CPAP treated infants. The reviewers of the use of prophylactic CPAP in the Cochrane library concluded that "A multicenter randomized controlled trial comparing prophylactic nasal CPAP with "standard" methods of treatment is needed to clarify its clinical role."[18]

In the post surfactant era, Verder et al conducted the first prospective evaluation of early CPAP (not necessarily delivery room CPAP) and short-term intubation for surfactant administration in a multicenter collaborative trial conducted from September 1991 to October 1992.[19] The primary hypothesis was that the use of early CPAP and brief intubation for surfactant in infants meeting pre-established criteria would reduce the percentage of infants requiring mechanical ventilation from 80% to 40%. Infants randomized to surfactant [Curosurf®] received 200 mg/kg, (2.5 ml/kg) following intubation, with manual ventilation for 2-5 minutes and were then extubated if stable. This study was stopped after an interim analysis demonstrated a significant benefit for the surfactant treated infants. Thirty-three of the 35 infants randomized to early surfactant were extubated after such treatment, and 13 required reintubation at a median of nine hours after surfactant treatment, compared with 28 of 33 control infants who were intubated a median of three hours after randomization, (p=0.003). The overall duration of ventilation in both groups was 2.5 days; there were no other differences between the groups. Verder et al performed a second multicenter prospective trial from April 1995 to January 1997 and enrolled infants <30 weeks with similar criteria to the previous trial, apart from an entry a/A ratio of .35 to .22, which decreased over 30 minutes, which was less stringent, allowing infants to be treated at lesser degrees of oxygen requirement, than their first study. These infants were initially all treated with CPAP and were enrolled up to 72 hours of age (median 4.1 hours, range 0.3 to 40.1hrs).This trial was also stopped after an interim analysis demonstrated a statistically significant reduction in the need for ventilation or death within seven days from 63% in the late-treated infants to 21% in early-treated infants. The median duration of ventilation in both trials was 2.5 days[20]. This study was not a prospective evaluation of early CPAP because CPAP was initiated in all infants at variable ages, and they did not evaluate infants of less than 25 weeks gestation.

Lindner et al recently reviewed their experience using a continuous prolonged (15 seconds duration) pressure controlled (20 to 25 cm H_2O) inflation of the lungs followed by continuous positive airway pressure (CPAP) of 4 to 6 cm H_2O for all ELBW infants immediately after delivery to establish a functional residual capacity (FRC) and to avoid intubation and ventilation[21]. The criteria for subsequent intubation were a $PaCO_2$ > 70 mmHg, an FiO_2 >.6 and respiratory distress with severe recurrent apnea. The rate of early intubation and mechanical ventilation in the delivery room decreased from 84% in 1994 to 40% in 1996. In 1996, 25% of the ELBW infants were never intubated (compared with 7% in 1994). There was no difference in mortality and overall there was less IVH > Grade 2 and BPD for the later cohort. No infant had an air leak upon admission to the NICU, suggesting that use of a prolonged inflation was well tolerated. Only 1 of 11 infants of 24 weeks gestation was able to avoid intubation in this study. Once again, there was no contemporaneous control group who did not receive delivery room CPAP. All of the above studies required high levels of $PaCO_2$ before initiating ventilation for this indication.

There is retrospective evidence suggesting a benefit for early CPAP in experiences from the USA. A survey of eight neonatology units in the USA in 1987 demonstrated that one unit, Columbia, had the lowest rate of CLD[22]. A more recent comparison of practices and outcomes between two neonatology units in Boston and the Babies and Children's Hospital unit (Columbia) evaluated VLBW infants born in 1991 to 1993.[23] This study revealed that 75% of infants at the Boston centers were initially treated with mechanical ventilation compared with 29% at Columbia, whereas initial CPAP was used in 63% of infants at Columbia vs. 11% at the Boston centers. Columbia also used less surfactant, 10% versus 45%, (all $p<0.001$). In addition the rates of CLD were significantly lower at Columbia compared to the other two centers (4% vs. 22%).

de Klerk and de Klerk recently published a five-year retrospective review of the outcome of 1 to 1.5 kg infants (n-116) treated with early CPAP vs. usual care (delayed CPAP)[24]. During 1996 -1998 infants were placed on CPAP within 10 minutes of admission (they did not describe the use of delivery room CPAP). Early CPAP beginning following admission to the neonatal unit decreased endotracheal intubation from 65 to 14%, $p<0.001$ and surfactant use (40 to 12%, $p<0.001$). Ventilator days were reduced from a median of 6 to 2 days ($p<0.01$) and oxygen supplementation or death at 28 days from 16 to 3%, $p<0.05$. Oxygen supplementation or death at 36 weeks did not significantly decrease (11 to 3% $p=0.25$). Ventilation and surfactant use were very high during the delayed CPAP (control period) so it is unclear whether other improvements in care may have coincided with the change to early CPAP.

Sandri et al[25] have recently published preliminary data from a multicenter randomized controlled trial of 155 infants 28 to 31 weeks gestation randomized to CPAP within 30 minutes of birth or to CPAP if the FiO_2 requirement exceeded 40%. Use of surfactant (22 to 21%, NS) and ventilator support (10 to 9%, NS) was not reduced with early CPAP. However, this trial included relatively bigger infants and the control group received CPAP at relatively low FiO_2, minimizing the difference between the experimental and control groups. This study did not evaluate the use of delivery room CPAP.

More recently Thomson et al presented the results of a multicenter trial of 237 infants from 27 to 29 weeks gestation[26], who were randomized to prophylactic surfactant followed by nasal CPAP using the Infant Flow DriverTM, early nasal CPAP followed by rescue surfactant, early IPPV with prophylactic surfactant, and conventional management. They reported that CPAP was initiated by 6 hours of age in 76% and 79% of the first 2 treatment groups, and those infants in the CPAP and rescue surfactant and prophylactic surfactant followed by CPAP groups required the lowest duration of ventilation. There were no differences in the incidence of CLD or other neonatal complications. Neither of these studies instituted the use of CPAP in the delivery room.

In a preliminary feasibility trial we have evaluated the ability of 5 sites of the NICHD Network to initiate CPAP during resuscitation, and continue its use in the NICU. In that study 103 infants were randomized to receive resuscitation with either CPAP/PEEP or no CPAP/PEEP. All infants were treated with CPAP following NICU admission. During delivery room resuscitation, 46 infants were intubated, 27 of 55 CPAP infants and 19 of 48 control infants ($p=0.33$). All 23 week gestation infants were intubated in the delivery room, irrespective of treatment group, whereas only 3 of 22 (13%) infants of 27 weeks required such intubation. When evaluated by birth weight, all 3 infants of less than 500 gm birth weight and 6 of 11 infants between 500-600 gm birth weights were intubated in the delivery room. All remaining infants were admitted to the NICU and had CPAP initiated. For infants not intubated in the DR, 36 infants were subsequently intubated in the NICU by day 7, 16 CPAP infants and 20 Control infants, ($p=0.21$). Infants in the CPAP group developed criteria for intubation sooner than the Control infants, with means and medians of 10.5 and 1.8 hours versus 20.7 and 3.3 hours,

p=0.41. These infants met criteria established for this trial which included an FiO2 > .3 to maintain an SpO2 > 90% or a PaO2 > 45 torr, an arterial PaCO2 > 55-60 with a pH < 7.25. or apnea requiring bag and mask ventilation. CPAP infants were intubated at an average FiO2 = 0.5 compared to 0.4 for control infants.

The literature thus suggests that early CPAP may be of substantial benefit, although none of this information has been obtained from prospective randomized trials of CPAP randomly applied in the delivery room to a population of VLBW or ELBW infants, with an appropriate control group. The terms early CPAP in the above studies (apart from that of Lindner et al[15]) involved the application of CPAP shortly following birth, not immediately after delivery. It is not surprising, therefore, that the recent revised NRP guidelines do not mention the use of CPAP/PEEP for neonatal resuscitation.[27] There is also some evidence that the level of CPAP needed may vary depending on the actual device utilized. Pandit et al and Courtney et al have demonstrated that variable flow CPAP was associated with a lower work of breathing and increased compliance at all levels of CPAP whereas constant flow nasal CPAP increased compliance only at 8 cm H2O.[28] In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.[29] A more recent trial compared the use of variable flow CPAP to conventional CPAP at extubation for 162 ELBW infants and reported no significant differences with either form of CPAP.[30] This study noted that 40% of ELBW infants failed extubation primarily because of apnea.

There are no studies in the surfactant and antenatal steroid era which have prospectively compared delivery room, CPAP with a more conventional approach, such as the use of prophylactic surfactant and conventional ventilation. The current available evidence demonstrates that prophylactic natural surfactant treatment significantly decreases mortality, air leak, and BPD in preterm infants.[31] Early surfactant, defined as surfactant at less than 2 hours of life is also of benefit and reduces air leaks, and mortality.[32] These reviewers noted that "early surfactant administration significantly reduces the risk of key clinical outcomes including pneumothorax, PIE, chronic lung disease, and neonatal mortality. Given the efficacy of prophylactic surfactant therapy (Soll 1999), this meta-analysis suggests that early selective surfactant administration to intubated infants with early signs of RDS may be part of a clinical spectrum of improved outcomes with earlier treatment". The most recent experience regarding early surfactant was presented by Horbar et al at the SPR in May, 2003. Their study which involved a cluster randomization in 57 NICUs of a practice to administer surfactant earlier compared with 57 control NICUs. They noted that infants at the intervention sites received their surfactant more often in the DR (54.7 vs 18.2%, p < 0.001) and earlier than the control sites (21 vs 78 minutes, p <0.001). There were no differences in mortality and pneumothoraces, the intervention centers had a lower rate of overall and severe IVH (28% vs 33%, p < 0.04, 10% vs 14%, p < 0.001) which were secondary outcomes of this trial.[33]

The most recent published study by Tooley and Dyke evaluated the use of prophylactic surfactant and early extubation to CPAP versus prophylactic surfactant and continuing management.[34] In this study 42 infants of 25 to 28(+6) wk of gestation were intubated at birth and given one dose of surfactant. They were then randomized within one hour of birth to either continue with conventional ventilation or to be extubated to nCPAP. They reported that 8 out of 21 (38%) babies randomized to nCPAP did not require subsequent re-ventilation. (Ventilation rates of 62% vs 100%, p = 0.0034). The smallest baby successfully extubated weighed 745 g. There were also significantly fewer infants intubated in the nCPAP group at 72 h of age (47% vs 81%, p = 0.025). There was no significant difference between the two groups in the number of babies that died, developed chronic lung disease or severe intraventricular hemorrhage. This study demonstrates that a significant number of very preterm babies with RDS can be extubated

to nCPAP after receiving one dose of surfactant. The current SUPPORT study will address this population, extended to 24 weeks, using a similar methodology for the infants of 24 to 27 6/7ths weeks who fail initial CPAP, with adequate power to determine if this approach is associated with significant benefits in terms of important short and longer term clinical outcomes.

Oxygen Saturation:

There is now an emerging body of information that suggests that many of the morbid conditions associated with extreme immaturity are potentiated by an excess of free-radicals occurring in infants who are intrinsically deficient in antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase. During hypoxia, metabolic alterations prime hypoxic cells to produce free oxygen radicals when subsequently exposed to oxygen. Such reperfusion injury, in addition to increasing the production of free oxygen radicals, is associated with other metabolic changes which may produce long lasting harmful effects. Silvers et al reported that a low plasma antioxidant activity at birth in premature infants was an independent risk factor for mortality.[35] Pulmonary oxygen toxicity, through the generation of reactive oxygen/nitrogen species in excess-of antioxidant defenses, is believed to be a major contributor to the development of BPD.[363738] For example the preterm macrophage showed a significant increase in cytokine mRNA and protein after overnight incubation in 95% oxygen compared with cells from term animals. Only macrophages from premature animals had a significant increase in intracellular oxygen radical content, measured by 2', 7'-dichlorofluorescin analysis, after incubation in 95% oxygen. This enhanced inflammatory cytokine response to oxygen has been postulated to be a mechanism involved in the early development of chronic lung disease in premature infants.[39] Varsila et al noted that immaturity is the most important factor explaining free radical-mediated pulmonary protein oxidation in premature newborn infants and that oxidation of proteins is related to the development of chronic lung disease.[40]

There are a number of prospective randomized trials that have compared the use of room air with 100% oxygen for neonatal resuscitation, and these have reported Infants resuscitated with room air resumed spontaneous breathing faster and required less positive pressure ventilation than infants resuscitated with oxygen.[41 42] Vento et al also demonstrated that that infants resuscitated with oxygen demonstrated long lasting evidence of oxidative stress and activities of superoxide dismutase and catalase in erythrocytes that were 69% and 78% higher, respectively compared with control infants resuscitated with room air at 28 days of postnatal life.[43] A recent meta-analysis of room air vs 100% oxygen resuscitation comprising of 1,693 infants in five trials revealed decreased neonatal resuscitation in infants resuscitated with room air (6 vs 11%, $p<0.005$ or 0.57 (95% CI 0.40 – 0.81))[44]. While these studies described results of mostly term infants, some infants were premature and the premature infant is known to have decreased antioxidants which would increase their susceptibility to oxygen toxicity. In the only randomized prospective trial to evaluate room air compared with oxygen in preterm infants, Lundstrom et al resuscitated infants of less than 33 weeks gestation who were randomized to receive either 80% oxygen or room air and noted that 2 hours following delivery, the room air infants had a higher cerebral blood flow compared with oxygen resuscitated infants. (median (interquartile range)): 15.9 (13.6-21.9) v 12.2 (10.7-13.8) ml/100 g/minute).[45] They did not find any significant differences in short or long-term outcomes but did note that SpO2 was lower in the room air infants with values at 5 and 7 minutes of 75% and 80% compared with 92% and 94% in the 80% oxygen group ($p<0.001$). Current monitoring with pulse oximetry using limits of 95 to 96% will result in significant periods wherein the infants actual PaO2 may increase to very high levels, as there are rapid increases in PaO2 with very small increments in SpO2 at this plateau portion of the hemoglobin dissociation curve.

Tin et al retrospectively reviewed outcomes for infants admitted to various neonatal intensive care units in northern England from 1990 to 1994 and managed with lower (70-90%) or higher SpO2 ranges (88%-98%).[46] They reported that infants who were managed for at least the first 8 weeks of life with SpO2s from 88-98% developed retinopathy of prematurity severe enough to be treated with cryotherapy four times as often as infants managed with the lower SpO2 ranges. Infants managed with the lower SpO2 ranges did not have increased risk of mortality or neurodevelopmental impairment. Bancalari et al using transcutaneous oxygen monitoring were able to show that infants who received continuous monitoring had a similar incidence of ROP to infants who were monitored by intermittent sampling had similar incidences of ROP, however for subgroup of infants $\geq$ 1100gm, there was a decrease in the incidence of ROP.[47] The STOP-ROP trial randomized infants with already established pre-threshold retinopathy and an SpO2 less than 94% to two ranges of SpO2 (89% to 94% versus 96% to 99%), for at least 2 weeks and until both eyes were at study endpoints. The higher range of SpO2 was associated with a non-significant decrease in the progression of ROP, but was associated with a greater need for oxygen and more exacerbations of BPD.[48]

Chow et al reported their observations following the institution in 1993 of a detailed oxygen management policy that included strict guidelines in the practices of increasing and weaning of fraction of inspired oxygen (FIO2) and the monitoring of oxygen saturation parameters in the delivery room, during in-house transport of infants to the NICU, and throughout hospitalization.[49] The main objectives were to avoid hyperoxia and repeated episodes of hypoxia-hyperoxia in very low birth weight infants. Their approach was initiated at birth, and included the avoidance of repeated increases and decreases of the FIO2, and a change in previously used alarm limits. They reported that following the implementation of these new management strategies that the incidence of ROP Grades 3 to 4 decreased consistently in a 5-year period from 12.5% in 1997 to 2.5% in 2001 and that the need for ROP laser treatment decreased from 4.5% in 1997 to 0% in the last 3 years. They adopted an SpO2 range of 85% to 95% for infants > 32 weeks gestation at birth, and a range of 85% to 93% for infants < 32 weeks. In addition some of their faculty used a range of 83% to 93%. This study did not provide any prospective values of the actual SpO2 ranges that were actually achieved in their infants, and thus it is uncertain whether their observed reductions in ROP were related to the altered SpO2 changes, or to overall changes in management over the period of the study. While these observations are encouraging, the authors did not report the complete neurodevelopmental outcomes for the infants cared for during the period of the new oxygen guidelines, and in the absence of contemporaneous controls, these results cannot be considered as proof that the SpO2 ranges used by this group are beneficial in terms of significant longer -term neurodevelopmental outcomes.

The most recent trial conducted in Australia compared SpO2 ranges of 91% - 94% versus 95% - 98% in 358 infants of less than 30 weeks who remained oxygen dependent at 32 weeks. The primary outcomes were growth and neurodevelopmental measures at a corrected age of 12 months. The high-saturation group received oxygen for a longer period after randomization (median, 40 days vs. 18 days; P<0.001) and had a significantly higher rate of dependence on supplemental oxygen at 36 weeks of postmenstrual age and a significantly higher frequency of home-based oxygen therapy. but resulted in an increased duration of oxygen supplementation.[50] They reported that additional oxygen supplementation did not improve survival, growth, or the occurrence of cerebral palsy at 18 to 24 months. Anderson et al have recently reported the results of a survey of pulse oximetry practices in 142 NICUs in the USA and noted a wide range of monitoring limits from 82% to 100%. They reported a lowered rate of ablative eye surgery in units that used lower maximal SpO2 limits, with the lowest range seen in units that had a maximum SpO2 of < 92%.[51]

In a recent review of oxygen toxicity in the premature infant Weinberger et al recommended that a strategy of limiting oxygen supplementation should be explored to reduce significant morbidities in the premature infant.[52] No studies to date have prospectively randomized ELBW infants to differing oxygenation ranges from birth onwards to determine if there is a benefit of lower versus higher saturation ranges.

1.5 Recent Relevant Studies

We have recently evaluated an FDA approved device specifically designed to facilitate neonatal resuscitation (Neopuff Infant Resuscitator, Fisher and Paykel, Auckland, New Zealand). This device has a t-piece that attaches to a mask and to a simple pressure generator. The inspiratory pressure can be set to a determined level, and a twist valve at the top of the t-piece determines the end-expiratory pressure. Most operators, with the exception of experienced respiratory therapists cannot routinely deliver a predetermined level of positive inspiratory pressures and PEEP[53] using an anesthesia-type manual bag and a neonatal manikin. In contrast, all operators could deliver the predetermined pressures with little intra-individual variation using the Neopuff®. The device operates identically using either a mask or endotracheal tube connection with or without PEEP/CPAP and the operator can adjust the positive inspiratory pressure (PIP) manually during resuscitation. At a flow of 10 liter per minute (lpm) or less, the maximum inadvertent CPAP/PEEP is 0.5 cm H_2O; which does not increase up to rates of 80 breaths per minute, the highest tested rate. The wave form is square, and is more similar to ventilator wave forms than to wave forms obtained using an anesthesia device. It should be noted, that the standard anesthesia devices used in delivery rooms may not deliver the desired CPAP/PEEP, depending on the operator's experience and skill, and may result in overshooting the desired PIP, even when the device is used by experienced operators. The Neopuff® device is now used as the standard resuscitation device in a number of hospitals in the USA, including at least two units in the NICHD Network.

There has been a recent trial evaluating earlier criteria for retinal laser ablative surgery for ROP, the ETROP study.[54] This study has demonstrated that using such criteria the visual outcomes are improved and reported that grating acuity results showed a reduction in unfavorable visual acuity outcomes with earlier treatment, from 19.5% to 14.5% (P=.01)and that unfavorable structural outcomes were reduced from 15.6% to 9.1% (P<.001) at 9 months. They recommend retinal ablative therapy for eyes with type I ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph); zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 ROP with plus disease. While these results are likely to be integrated into Network practice, there is currently no baseline data regarding the number of infants who would meet these criteria, and thus we will utilize the presence of Stage 3 or greater ROP and/or the receipt of retinal surgery to power our current trial.

2.1 Study Design

This will be a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. The individual factors to be tested will be:

1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early ($\leq$ 1 hour) surfactant and mechanical ventilation.

2) A prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant is no longer requiring ventilatory support

or oxygen.

The oxygen saturation monitoring portion of our study will be designed to parallel the planned POST-ROP trial, a multicenter, multinational prospective trial to evaluate different SpO2 levels from birth.[55] The methodology described under oxygen monitoring (**Section 4.1B**) was developed for the current protocol to allow a blinded comparison of 2 different SpO2 levels using specially designed pulse oximeters. These devices have been developed by the Masimo Corporation (Irvine Ca) and tested prior to initiation of this trial, and the POST-ROP study group has agreed to use the ranges described in this protocol, and the methodology that will allow the oximeters to provide actual SpO2 values when the SpO2 is < 85% and > 95%(Personal communication, Cynthia Cole 2004). This methodology will provide the clinicians and caretakers with the infants' actual SpO2 values during hypoxia and hyperoxia, within the current parameters of clinically accepted practice.

Please see **Section 8.2** for further Tables describing details regarding the projected outcomes relative to the study interventions

Randomized Intervention	**Low SpO2 85% to 89%**	**High SpO2 91 to 95%**
Treatment **Early CPAP**	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control **Prophylactic/Early Surfactant**	Control + Low SpO2	Control + High SpO2

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

2). We hypothesize that that relative to infants managed with a higher SpO2 range that the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

2.3 Secondary Hypotheses

We hypothesize that the use of continuous positive airway pressure (CPAP) with a permissive ventilator strategy and/or a lower SpO2 range starting at birth in the delivery room will result in the following:

- A decreased Mortality/NDI at 18-22 months corrected age.

- A decreased frequency of endotracheal intubation before 10 minutes of age
- A decrease of the total duration of mechanical ventilation during the entire NICU stay
- A decreased incidence of surfactant treatment
- A decreased incidence of air leaks on admission and overall
- A decreased duration of intubation
- A decreased duration of mechanical ventilation
- A decreased duration of oxygen supplementation
- A decreased duration of the percentage of pulse oximetry values > 90%
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- A decrease in the percentage of infants who receive postnatal steroids to prevent or treat BPD
- A decreased incidence of BPD at 36 weeks using the physiologic definition of BPD
- A decreased incidence of ROP or Stage 3 ROP
- A decreased incidence of necrotizing enterocolitis (NEC)
- A decreased incidence of IVH and severe IVH
- A decreased incidence of periventricular leukomalacia
- A decreased incidence of neurodevelopmental impairment at 18-22 month follow-up
- A decreased incidence of cerebral palsy at 18-22 month follow-up

3.1 Study Population

Study subjects are infants of 24 0/7ths to 27 6/7th weeks at birth for which a decision has been made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) will be enrolled because over 80% of such infants in the Network are intubated, usually early in their neonatal course. It is important to note that previous studies have included few, if any infants less than 25 weeks gestation and such infants are not included in the current COIN trial or the proposed Vermont Oxford Trial. Such infants will be enrolled in this trial because they are the group of infants with the highest mortality and morbidity. The feasibility trial demonstrated that the 5 NICHD centers involved could reduce intubation in the delivery room to less than 50% of such infants if they are not intubated for surfactant. We will exclude infants of 23 weeks or less in view of their extremely high mortality and morbidity, and their almost universal need for delivery room intubation for resuscitation. We have included Tables at the end of the protocol utilizing infants from 23 to 28 weeks to demonstrate that our sample size estimates will not be adversely affected if we should choose to include infants of 23 and/or 28 weeks.

Strata: There will be 2 randomization strata, infants of 24 0/7ths to 25 6/7ths weeks, and infants of 26 0/7ths-27 6/7ths weeks by best obstetrical estimate. The purpose of stratification is to assure an appropriate distribution of risk among the four study arms. The study will not be powered to detect outcome differences between strata.

3.2 Inclusion Criteria

- Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
- Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Infants whose parents/legal guardians have provided consent for enrollment, or
- Infants without known major congenital malformations

3.3 Exclusion Criteria

- Any infant transported to the center after delivery
- Infants whose parents/legal guardians refuse consent
- Infants born during a time when the research apparatus/study personnel are not available
- Infants < 24 weeks 0 days or ≥ 28 weeks 0 days, completed weeks of gestation

3.4 Sampling Recruitment and Screening Procedures

Infants will be recruited for this study by approaching one or both parents at the time of admission to the hospital where there is deemed to be a risk of premature delivery at 27 6/7ths weeks or less.

3.5 Screening Procedures

All admissions for threatened premature delivery will be screened on a daily basis to ensure that eligible patients can be enrolled. We will inform our obstetrical colleagues at each involved institution of the nature of this study, and encourage them to discuss this study with their patients at risk of premature delivery. The study coordinator at each site will maintain a screening log of potentially eligible patients. In addition the usual practice of neonatal consultation for all such at risk deliveries will provide a second opportunity to approach mothers with fetuses at risk of preterm delivery

3.6 Other Procedures

A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology will be used at all sites for the delivery room administration of CPAP. A training video to explain the proper use of the Neopuff® will be provided to any site which wishes to use it and is not familiar with the device.

3.7 Randomization

Randomization will be stratified by gestational age group, will occur prior to delivery for consented deliveries, and will be performed by utilizing specially prepared double-sealed envelopes. Deliveries will be randomized as a unit, thus multiples, twins, triplets etc will be randomized to the same arm of the trial. We believe that this methodology will improve the percentage of consents, since in previous trials parents of multiple infants have expressed concern that their infants were being randomized to different treatment arms. We have made an appropriate sample size adjustment to account for this clustering effect.

Each randomization will indicate either Treatment Group (CPAP and permissive ventilation management) or Control Group (Prophylactic/Early surfactant and conventional ventilator management) and either the Low (85%-89%) or High (91% - 95%) SpO2 group. Parents will be approached for consent before delivery, but the randomization envelope will only be opened when delivery is imminent for a consented family.

The Pulse Oximeters (PO) will have unique identifying labels and the oximeter specified in the randomization will be identified by a unique number which will match the number of the study Pulse Oximeter assigned for that infant. All caretakers including the coordinators will be blinded to the Pulse Oximeter range, and an identification code for each site will be maintained by the PI/Site Coordinator should identification be required for patient safety. RTI will work with Masimo to ensure that the POs are labeled with unique identifiers, whose code will identify the

actual range of the individual PO. These would be affixed prior to shipping to the sites, and a copy of the labels sent to the site would be provided to RTI.

This methodology should reduce the work load to the sites at the time of randomization, providing the care team with the information needed for the infants' randomization, and will allow the study center to be notified within 24 hours of any randomization.

3.8 Informed Consent:

Parents will be approached prior to delivery for informed consent, and their infants enrolled at delivery. As previously noted we will randomize by family, thus all offspring will be randomized to the same trial arms, provided adequate equipment and personnel are available at the time of delivery.

3.9 Management and Retention of Study Population

All enrolled infants will be seen at follow-up-up at 18 to 22 months corrected age. We do not anticipate a significant loss other than death (13% in the first 12 hours , approximately 32% before discharge, based on year 2000 registry data), and will plan for a further 15% attrition.

4.1 A: Study Intervention: Mode of Ventilatory Support

The intervention will begin after birth when the infant is given to the resuscitation team. The conduct of the resuscitation will follow usual guidelines, and once stabilized, all Control infants in both strata will receive prophylactic/early surfactant (within 1 hour of age) whereas all Treatment infants will be placed on CPAP/PEEP following stabilization, and be intubated only for resuscitation indications.

The assignment to either a high or low SpO2 by study oximeter assignment will be performed immediately following NICU admission, with a maximum allowable delay of 2 hours following NICU admission.

TREATMENT: CPAP Group : Early Extubation and CPAP

Delivery Room Management

FiO2:

Standard of care.

CPAP:

CPAP or ventilation with PEEP will be utilized if the infant requires positive pressure during resuscitation. CPAP will be continued until admission to the NICU using the Neopuff or equivalent device and a face mask or nasal prongs. Initial PPV will be at a PIP of 15-25 cm H_2O and a PEEP/CPAP of 5 cm cmH_2O.

Intubation:

Infants may not be intubated for surfactant only in the DR. Infants who require intubation for resuscitation will receive surfactant within 60 minutes of birth.

Intubation will be performed only for the standard NRP indications including failure to respond to PPV with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determines that surfactant is urgently required.

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

NICU Management

These infants will be managed on nasal CPAP, and intubation is never required by protocol. They *MAY* be intubated if they meet ***ANY*** *of* the criteria listed below. If intubated within the first 48 hours of life they should receive surfactant

Intubation:

- An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) documented on a single blood gas within 1 hour of intubation
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation.)

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

These criteria will continue in effect for a minimum of 14 days of life.

Intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.
(e.g. - Upper airway obstruction (choanal atresia, micrognathia/glossoptosis)).

Extubation:

An intubated CPAP-Treatment infant ***MUST*** *have extubation attempted within 24 hours if* **ALL** *of the following criteria are met and documented on a single blood gas*

- $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples)
- An indicated SpO2 $\leq$ 88% with an FiO2 $\leq$ 50%
- A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving ionotropic/vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA

These criteria will continue in effect for the first 14 days of life.

Failure to extubate an infant meeting all of the above criteria will be recorded as a study protocol violation unless extenuating circumstances are noted. (e.g. - PIE, airleak)

Reintubation

If a Treatment infant is extubated as per Protocol Criteria, and requires re-intubation for any indication, any further attempt at extubation may be delayed for 24 – 48 hrs based on the clinician's decision.
Re-intubation criteria are the same as those for Intubation for the CPAP infants. Thus, intubation is not required, but these infants **MAY** be reintubated if they meet **ANY** of the following:

Re-Intubation Criteria:

- An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) for 2 successive blood gases at least 15 minutes apart.
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation as noted above on page 13)

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Re-intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.

D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be discontinued earlier and follow unit Standard of Care. CPAP may be restarted at any time in such infants.

CPAP infants who require intubation three times, for any criteria, will have all subsequent treatment including subsequent extubations and any further re-intubations performed using unit Standard of Care. This addition is to prevent such infants from being exposed to further protocol driven intubations and extubations.

Surfactant

Infants intubated in the first 48 hours for respiratory distress should be given a minimum of one dose of surfactant
Up to 4 surfactant administrations may be given if the FiO2 is greater than 50% following manufacturers' recommendations for dose and dosing interval.

Explanation:

The purpose of the above criteria is to minimize the duration of intubation of Treatment infants. The Criteria for extubation are more severe than those of the Control Group infants, and extubation must be attempted for any infant who fulfills the stated criteria.

The criteria for re-intubation recognize that intubation is traumatic, and is designed to avoid frequent attempts at extubation for infants who fail.

CONTROL- Prophylactic/Early Surfactant and Ventilation

Delivery Room Management:

Infants will be intubated in the delivery room and given surfactant or receive surfactant

within 60 min minutes of birth. The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

NICU Management:

Extubation:

An intubated Surfactant-Control infant will continue to receive mechanical ventilation until extubation criteria are satisfied, but **MUST** have Extubation attempted within 24 hours of fulfilling ***ALL*** of the following criteria documented on a single blood gas.

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 = 35 with a SpO2 > 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving ionotropic / vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA (Defined as bounding pulses, audible murmur and Echo confirmation of L-R shunting with increased LA/Ao size

These criteria will continue in effect for a minimum of 14 days for all infants.

Failure to attempt to extubate an infant meeting all of the above criteria, or extubation prior to reaching criteria, will be recorded as a study protocol violation unless extenuating circumstances are noted.

Weaning

This protocol will not define strict weaning criteria for the Control infants, but it is to be understood that reasonable attempts should be made to extubate these infants. While it is understood that some centers may be using somewhat more severe FiO2 and PaCO2 criteria than those listed here as current practice, these Criteria are thought to reflect current Network practice and practice at 2 of the 3 Best practice centers.

Reintubation:

- Control Infants may be reintubated using Standard of Care.

Explanation:

Control infants are to be treated using an approach considered similar to current standards of care. Apparatus for resuscitation for Control Infants at each center will represent their usual equipment for the resuscitation of an ELBW infant. The Neopuff may be utilized for such infants as above, but this is not mandatory. It is anticipated that the majority of these infants will be intubated and receive surfactant in the delivery room.

4.1 B: Study Intervention: Low versus High SpO2 Range:

There will be 2 ranges of SpO2 utilized during this trial. The Low target range will be 85% to 89% and the High target range will be 91% to 95%. The altered Pulse Oximeters (PO) are described below, and will display a range of 88% to 92% when the SpO2 ranges are in the Target ranges indicated above. Thus a Low range PO will read 88% when the actual SpO2 is

approximately 86%, and 92% when the actual SpO2 is 89%. Similarly the High range PO will display 88% when the actual SpO2 is 91% and indicate 92% when the actual SpO2 is approximately 95%. See below for further explanation. This deviation is similar to the BOOST trial which used a continuous 3% offset.[42] As an added safety feature, the POs used in this trial will revert to the actual SpO2 values and allow the caretakers to be aware of actual SpO2 values < 85% and > 95%.

Low Range Infants:

These infants will be monitored with a target SpO2 range of 85% -89% with suggested indicated alarm limits of 85% and 95%, representing approximately a 10% span for alarms as long as the infants are receiving any ventilatory support, CPAP, and/or supplemental oxygen. **The study pulse oximeters will be applied to the infant within two hours following NICU admission.** The assigned PO will remain on the infant and will be removed once the infant has been in room air and off ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA.

High Range Infants:

These infants will be monitored with a target SpO2 range of 91% -95% with suggested indicated alarm limits of 85% to 95% representing approximately 10% span for alarms as long as they are receiving any ventilatory support, CPAP and/or supplemental oxygen. The study pulse oximeters will be removed once the infant has been in room air for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA.

These interventions will be delivered using specially developed pulse oximeters whose displays (the actual readings seen by caretakers) will be adjusted so that the randomized range of SpO2 (either 85%-89%, or 91%-95%) will be indicated by a range of 88%-92%. This is done by progressively altering the offset as the alarm limits are approached, and Masimo has confirmed that this technology is workable. The target oxygen saturation (88-92%) of the display will be the same in both groups as indicated in Table1 below.

These POs will be able to display trend plots of the SpO2 display for a preceding interval to allow the caretakers to receive feedback regarding the actual SpO2 ranges of their baby.

The suggested alarms limits will be 84% and 96% for both groups.

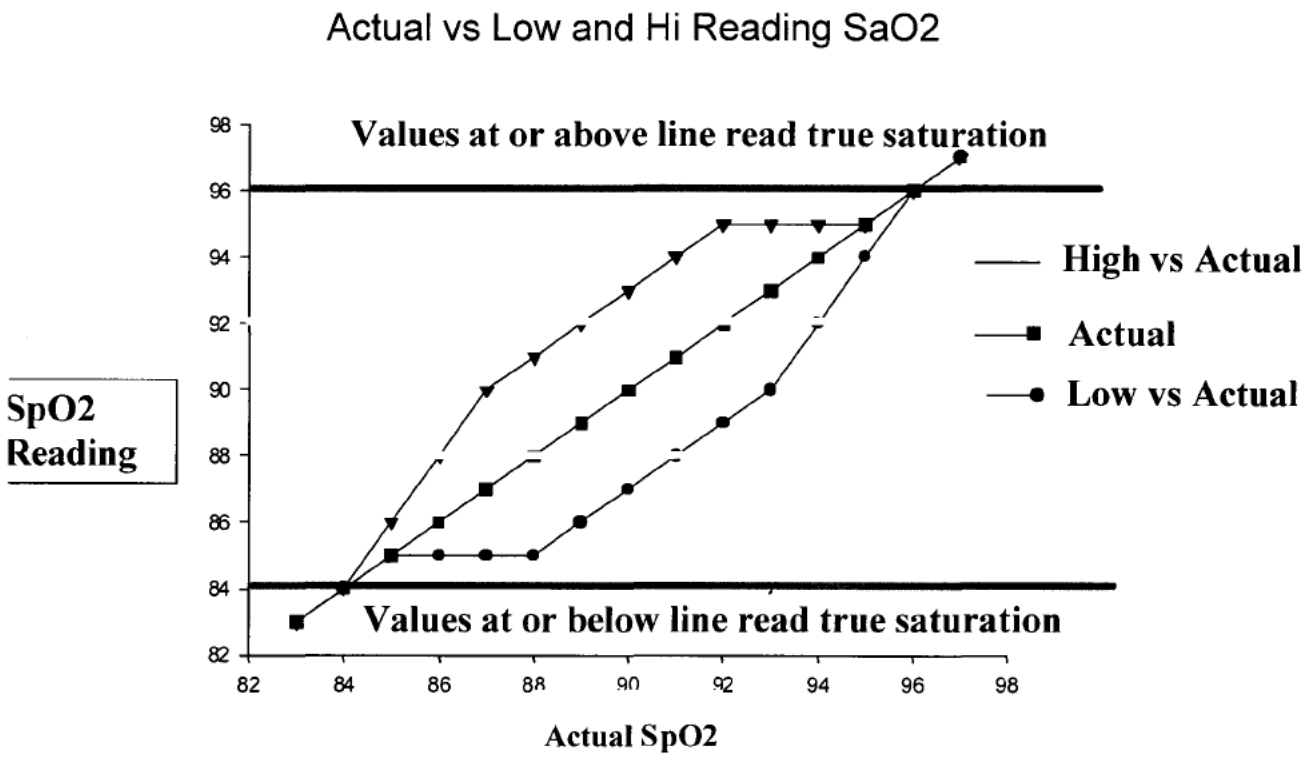
Table 1. Output and Actual SpO2 Targets and Alarms

SpO2 Group	Displayed Target	Actual Target	Alarm Values
Low SpO2	88-92%	85-89%	<85 and >95%
High SpO2	88-92%	91-95%	<85 and >95%

The pulse oximeters will display the actual reading when then the SpO2 is below 85% and above 95%. This will provide for an overall set of limits on actual SpO2 of 84% to 96% which we believe will avoid unacceptable levels of hypoxia, (< 85%) and hyperoxia (> 95%) **All data below 85% and above 95% will be unaltered on all oximeters**. An averaging time of 16 seconds will be applied in keeping with the settings used by POST-ROP. The preset alarm

delay will be 10 seconds. The fail-safe alarm will alarm whenever the reading is 5% below the low alarm limit, in the study this will be at 80%. Some network centers use an averaging interval of 30 seconds, others use very short averaging times. This setting will allow for appropriate response times without unmasking the caretakers.

We believe that this methodology will provide an acceptable ethical design for this trial. The diagram below demonstrates how the pulse oximeter readings are altered between values of 85% to 95%. Readings below or above these levels will not be altered, and will represent actual SpO2 as determined by the pulse oximeter. Note that the entire range of actual SpO2 is altered to either a lower (Low SpO2 Group) value or higher value (High SpO2 Group) till the ends of the alarm ranges of 85% and 95% which will ensure that the infants SpO2 will be separated throughout this range.



Every 30 days until 36 weeks PCA or until the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per 10 seconds of monitoring) will be downloaded and transmitted to RTI for subsequent analyses. (This interval of sampling may change to a less frequent interval for the convenience of the study personnel, without losing significant data). These data points will be used to confirm that the infants were managed at the target ranges and provide objective confirmation of the SpO2 Group assignments. The technology for downloading and interpreting this data was used in the DR CPAP Pilot trial, but recent technology utilizing a software program (Profox, Profox Inc, Escondido, Ca) which has been written to facilitate this process, will dramatically simplify this procedure.

Non-study pulse oximeters cannot be used on enrolled patients. If a second oximeter is

required for such a patient, the site coordinator will provide an identical oximeter for the patient.

All ventilatory care after 14 days of age will follow the standard of care for each unit. Each unit will provide guidelines for their approach to continuing mechanical ventilation.

4.2 Delivery of Interventions

CPAP/PEEP in the DR

CPAP and positive pressure ventilation (PPV) in the delivery room for Treatment infants will be administered via a T-piece resuscitator, a neonatal ventilator or an equivalent device that is currently used by the site for the delivery of CPAP. (See **3.6**).

Use of Nasal SIMV;

This approach is currently used by some Network units and has been previously established as being superior to CPAP following extubation in three prospective trials.[56,57,58] For uniformity nasal SIMV may be used in place of CPAP ***only following extubation for both Treatment and Control infants.***

Use of Caffeine:

Caffeine may be administered 2 hours prior to planned extubation, and for any clinically significant apnea.[59]

Surfactant Type:

All centers are asked to follow current unit practice in determining the type of surfactant utilized, and manufacturers' recommendations for redosing intervals.

The protocol requires that at least one dose of surfactant be administered to any infant intubated within 48 hours of birth, with evidence of respiratory distress, who has not previously received surfactant.:

Postnatal Steroids

Postnatal steroids for the purpose of preventing or treating BPD/CLD will be prohibited for any infant in this trial in the first 21 days of life. Hydrocortisone for hypotension may be used as noted below.

If postnatal steroid use is considered after 21 days of life for any infant for the prevention/treatment of established lung disease the following guidelines should be followed:

1. The AAP statement and recommendations regarding Post-natal steroids should be adhered to.[60]
2. The lowest dose of dexamethasone considered effective should be used and if ineffective after 24 – 48 hours they should be stopped.
3. Consider using hydrocortisone as a first therapy at a dose of 1 -2 mg/kg/day before using dexamethasone.
4. For hypotension, hydrocortisone in a dose of 1 mg/kg/dose should be given after fluid administration and standard doses of ionotropes/pressors have failed to correct the low blood pressure.

Head Ultrasound

If a Head ultrasound is done between days 4 and 21 the results will be recorded for this study. If one is not done for standard of care, the study requires that at least one HUS be completed during this window

4.3 Protocol Violations:

The occurrence of any one of the following criteria will determine whether an individual infant will be considered a protocol violation:

1. Intubation of a treatment group infant in the DR for the exclusive purpose of giving surfactant, in the absence of bradycardia (HR< 100 bpm) and/or poor color or an SpO2< 85-90% in an infant with adequate spontaneous respirations or receiving adequate ventilation
2. Failure to continue CPAP on admission to the NICU for a treatment infant requiring supplemental oxygen
3. Intubation and surfactant administration of a treatment infant without meeting stated protocol criteria.
4. Failure to extubate a Treatment infant who fulfills all the extubation criteria.
5. Extubation of a Control infant who does not meet any of the Extubation criteria.

All protocol violations will be reviewed by the center PI who will discuss each protocol violation with the involved clinicians and provide a written summary including steps taken to avoid future violations.

4.4 Adverse Events

Serious and unanticipated adverse events may be anticipated in this vulnerable population. Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

These outcomes will be evaluated on a monthly basis by RTI, and if the incidence of any of these outcomes is determined to be 5% - 10% greater in any arm of the study, this information will be provided to the Study PI and committee and the DSMC for immediate consideration, and evaluated for consideration of termination of the study or treatment arm.

4.5 Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. Obrien-Fleming [61] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock [62] boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

5.1 Measurement Methods:

The PO stored data will be retrieved using a routine provided to all site coordinators, and the resultant data file will be sent electronically to RTI to be included as part of the study data collection.

5.2 Schedule of Data Collection: (See Data tables in Appendix A)

5.3 Primary and Secondary Outcome Measures

5.3.1 Primary Outcome Measure

The primary outcome will be the percentage of infants surviving without BPD (using the Physiologic Definition) or severe ROP (threshold disease or the need for surgery).

5.3.2 Secondary Outcome Measures

- The five minute Apgar score
- The percentage of infants with death or neurodevelopmental impairment at 18 months
- The total duration of mechanical ventilation during the entire NICU stay
- The percent of infants alive and off ventilation by day 7
- The proportion of infants receiving surfactant treatment
- The incidence of air leaks on admission and overall
- The incidence of BPD at 36 weeks using the physiologic definition of BPD
- The incidence of death
- The proportion of infants with severe IVH
- The proportion of infants with PVL
- The proportion of infants with threshold ROP and requiring surgery for ROP
- The proportion of infants requiring endotracheal intubation before 10 minutes of age
- The proportion of infants with of air leaks on admission and overall
- The duration of oxygen supplementation
- The percentage of pulse oximetry values > 90%
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- The proportion of infants who receive postnatal steroids to prevent or treat BPD
- The proportion of infants with who develop necrotizing enterocolitis (NEC)
- The proportion of infants with cerebral palsy at 18-22 month follow-up

6.1 Training Study Personnel

6.1.1 Job Descriptions of Study Personnel

The NICHD coordinators will assist the respiratory therapists in each unit regarding the set up the equipment for the delivery of CPAP in the delivery room, and in the NICU.

6.1.2 Training of Personnel

There will be a training session held in Cincinnati about the delivery of CPAP in the delivery room and in the NICU, and a review of available devices that may be used for this intervention.

7.1 Data Collection and Management

We will develop the required CRFs as per Network procedures. It will be our aim to minimize these to ensure that data is collected regarding the intervention, the adherence to the protocol for intubation, surfactant administration, and extubation, and the occurrence of the primary and secondary end-points. All remaining information will be extracted for the current data forms.

8.1 Statistical Analysis

8.1.1 Analysis Plan

The primary analyses of this factorial trial will be a logistic regression analysis of the percent of each Group (Treatment vs Control, High vs Low SpO2) who developed their respective outcome measure (survival without BPD or ROP at 36 weeks respectively). An important analysis of a secondary outcome will determine if there is an effect of the interventions on the percent infants who survive without neurodevelopmental sequelae at 2 years For all secondary outcomes, univariate analysis for continuous variables will be performed using parametric (e.g., Student t tests, ANOVA), and non-parametric (e.g., Mann-Whitney U) tests where appropriate; categorical variables including the primary outcome, feasibility, will be examined by Chi square analysis. Analysis of covariance and multiple regression models will be used to examine the interaction between, and the independent effects of, various factors, (e.g., birth weight, gestational age, gender, treatment group, center, etc.) upon secondary outcomes (i.e., time to improvement in oxygen saturation, duration of positive pressure ventilation, five minute Apgar score, duration of mechanical ventilation, surfactant requirement, incidence of air leaks, and incidence of BPD).

8.2 Sample Size

As discussed above, there are two main outcomes for the factorial design: mortality or BPD; mortality or ROP. Mortality or NDI is a secondary outcome. For the cohort of infants born in 2000, 401-1000g birth weight, we have the following prevalence of outcomes for four subgroups of that cohort: Please note that we used population groupings to include or exclude infants of 23 and 28 weeks. These additional groups do not change the sample size estimates as the outcomes are essentially similar.

Subgroup	Death/BPD	Death/> Stage III ROP	Death/NDI
23-27 GA	70.6	53.1	65.7
24-28 GA	64.8	44.5	59.3
24-27 GA	66.6	46.8	60.7
23-28 GA	68.6	50.4	64.0

If the study is powered for the two outcomes, Death/BPD and Death/>Stage III ROP, then the sample size is driven by the prevalence nearest 50% for a given absolute percentage detectable change in the outcome. In this case it's the Death/>Stage III ROP outcome with a range of 44.5% to 53.1% across the subgroups. Furthermore, the sample size depends on the outcome rate only through the standard deviation of the rate and this turns out to be essentially

50% for all subgroups (i.e. ranges from 49.7% to 50.0%). Hence one sample size table suffices for all.

Hence, for any of the four groups the table below gives the total sample sizes required for a range of absolute percent changes, a two-tailed alpha level test of 5% and for powers of 80% and 90%. The N1 column powers the 2 x 2 factorial for the two primary outcomes and the N2 column assures comparable power for the Death/NDI outcome.

With regard to the power for detecting the interaction between the two factors in the factorial, a fourfold increase in the stated sample size would be required to detect an interaction effect as large or larger as that stated in the table (i.e. the Detectable Difference), assuming the same alpha level and power. The interaction effect referred to is the classical one where the difference in outcome for one of the treatments in the factorial differs according to the level of the other treatment (i.e. the treatment effects are not additive).

If the study is powered for the two primary outcomes and mortality/NDI is considered as a secondary outcome then the table below gives the total sample size required for a 5% overall level test at 80% and 90% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and a conservative outcome rate of 50% in making the calculations. These sample sizes are given in the N1 column and would also allow a 10% difference in NDI/death to be detected with a power of 73%. If an 80% power is desired for the NDI/mortality outcome this would result in sample sizes in the N2 column.

TOTAL SAMPLE SIZES REQUIRED

	80% Power		90% Power	
Detectable Difference (absolute %)	Total N1*	Total N2**	Total N1*	Total N2**
8%	1792	2096	2284	2676
9%	1388	1624	1792	2096
10% (multiples to same arm)	1120	1312	1456	1704
11%	940	1104	1208	1416
12%	784	920	1032	1208
13%	672	788	860	1008
14%	584	680	756	880
15%	504	588	652	768

* sample sizes to insure the appropriate power for the two primary outcomes (BPD/Death, ROP/Death)

** sample sizes to insure the appropriate power for the secondary outcome (NDI/Death)

We have increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduces a clustering effect into the design. The analysis of the GDB data base resulted in the 1.12 estimate. We also inflated the sample sizes by 17% to adjust for attrition after discharge and before follow-up. This figure was also determined from the GDB data base. Thus the actual sample size for this trial would be 1310 for 80% power for detecting an absolute difference of 10% in the two primary outcomes and the NDI secondary outcome. This sample size is not sufficient to permit detection of interactive effects between the two treatments with reasonable power.

HYPOTHESIZED TREATMENT EFFECTS FOR SUPPORT

When sample sizes were estimated for the SUPPORT trial the following base rates for the three outcomes (rounded) were calculated from the GDB:

--BPD/Mortality—67%
--ROP $\geq$ Grade III/Mortality—47%
--NDI/Mortality—61%.

Sample sizes were calculated for a range of absolute treatment effects and 10% seemed to be the smallest plausible effect for the study. Rounding the above rates to 65, 45, and 60 percent the following tables show what the data would look like under the assumption of a 10% reduction in outcome and control rates of 65, 45, and 60 percent for the DRCPAP (No)/ SpO2 (High) group. Interactive effects are assumed to be zero. Tables are presented which show treatment effects when both treatments affect the BPD and the ROP outcomes and when only one of the treatments affects outcome. The NDI table is only for the case where both treatments affect outcome.

Table IA

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on BPD/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO2

CPAP	Low	High	Overall
Yes	45	55	50
No	55	65	60
Overall	50	60	55

Table IB

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on BPD/Mortality **Assuming a 10% Main Effect for CPAP Only**—Table Entries are Outcome Rates (%)

SpO2

CPAP	Low	High	Overall
Yes	55	55	55
No	65	65	65
Overall	60	60	60

Table IIA

Treatment Effects for SpO2 (High, Low) and DRCPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO2

SpO2

CPAP	Low	High	Overall
Yes	25	35	30
No	35	45	40
Overall	30	40	35

Table IIB

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for SpO2 Only**—Table Entries are Outcome Rates (%)

		SpO2		
		Low	High	Overall
CPAP	Yes	35	45	40
	No	35	45	40
	Overall	35	45	40

Table III

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on NDI/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

		SpO2		
		Low	High	Overall
CPAP	Yes	40	50	45
	No	50	60	55
	Overall	45	55	50

9.1 Quality Control

The selection of personnel will be left to the site PI's. No specific job descriptions are required for this protocol. The actual duties of the individual who will perform the randomization will be detailed in the manual for the study. Protocol violations will be reviewed, and if frequent, may require a site visit and consideration for termination of a collaborating site.

10.1 Risks and Benefits

Potential risks to the use of CPAP and/or PEEP include pneumothoraces; however this is unlikely to be increased over the risk of PPV alone. The level of CPAP/PEEP will be set at 5-6 cmH_2O, a level that is not thought to increase the incidence of pneumothorax. Recent data from Dr Morley suggest that this level is probably the lowest effective level especially when the infant's mouth is open, and is well tolerated. Objections to use of PEEP or CPAP could be countered by the argument that the majority of neonatologists use PEEP in resuscitation, thus the standard of care at most centers probably include the administration of CPAP and/or PEEP. Another potential risk is the administration of CPAP in the DR to infants without respiratory distress, which could conceivably cause vagal stimulation and resultant bradycardia and gastric distension.

Perhaps the major risk of this trial is that the known benefit of early surfactant with a reduction of death and disease severity, and a reduction of BPD with natural surfactant may not be offset by the early use of CPAP. However, the increasing trend in the use of early CPAP without such evidence represents an even greater risk.

Appendix A

Study Tables

Table 1. Patient Description

	Treatment	Control	P Value
Birth weight (grams) (M + SD)			
Gestation (weeks) (M + SD)			
Apgar 1 min < 3 Assigned			
Apgar 5 min < 3 Assigned			
Received PPV (Number, %)			
Surfactant in DR (Number, %)			
Received Chest Compression (N%)			
Received Epinephrine (N, %)			

Table 2. Other Outcomes

	Treatment	Control	P Value
Total Duration of Mechanical Vent (M +SD)			
Duration of Oxygen (Total days)			
Duration of CPAP			
Duration of nSIMV			
% alive off MV by Day 7 (+SD)			
Pneumothoraces (N, %)			
Other air leaks (N, %)			
BPD at 36 weeks (O_2 dependence)			
BPD by Physiologic Definition (N%+SD)			
Survived to discharge (N,% +SD)			
Number Never Intubated (N, %)			
Number receiving PNS for BPD (N, % %)			
Alive without neurdevelopmental impairment at (18-22 months) years (N, %, +/-SD)			

Appendix B

Study Tables

Table 1. Patient Description

	Low Saturation	High Saturation	RR	CI	p value
Birth weight (grams) (M + SD)					
Gestation (weeks) (M + SD)					
Race (W, B, H, other) %					
Antenatal steroids (%)					
Apgars ≤3 at 5 min					

Table 2. Primary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Threshold ROP/Surgery or death by 36 weeks (%)					
Death by 36 weeks (%)					
Threshold ROP in alive infants at 36 weeks (%)					
BPD or Death by 36 weeks (%) ±					

Table 3. Secondary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Death by discharge status (%)					
BPD in alive infants at 36 weeks (%)					
IVH 3 or 4/PVL or death by 36 weeks (%)					
IVH 3 or 4 in alive infants at 36 weeks (%)†					
Cystic PVL in alive infants at 36 weeks (%)†					
Neurodevelopmental impairment or death by 18-22 months (%)					
Death by 18-22 months (%)					
Neurodevelopmental impairment at 18-22 months (%)†					
Cerebral palsy at 18-22 months (%)†					
MDI < 70 (%)					
PDI < 70 (%)					
Any blindness at 18-22 months (%)†					
Unilateral blindness at 18-22 months (%)†					
Deafness at 18-22 months†					

†Analyzed for survivors

Table 4. Other Outcomes

	Low Saturation	High Saturation	RR CI	P Value
Total Duration of Ventilation (M+SD)				
On ventilator or death by day 7 (%)				
Pneumothorax (%)				
Any air leak (%)				
Postnatal steroids for BPD (%)				
Necrotizing enterocolitis ≥2 (%)				
PDA requiring surgery				

	Early CPAP/Early Extubation	Prophylactic Surfactant
Delivery Room Management	Resuscitate using CPAP. If necessary, initial PPV settings PIP 15-25, PEEP 5. Transport on CPAP If intubated for resuscitation, give surfactant within 1 hour of age. Do not intubate unless indicated by NRP guidelines	Intubate and give surfactant within 1 hour of age Transport with PPV according to SOC
Upon NICU Admission	Randomize within 2 hours to Pulse Oximeter	Randomize within 2 hours to Pulse Oximeter
Intubation Criteria	**Not Required. May intubate for ANY of these criteria** • FiO_2 >.50 required to maintain indicated SpO2 ≥ 88% (using the altered Pulse Oximeters) for one hour • $PaCO_2$ > 65 torr (art. or cap. samples, if venous $PaCO_2$ > 70 torr) documented on a single blood gas • Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. **If intubated, give surfactant within the first 48 hrs if in respiratory distress**	**Reintubation Criteria** **Standard of Care**
Extubation Criteria	**Attempt extubation within 24 hours of fulfilling all of the following criteria:** • $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples) • An indicated SpO2 ≥ 88% with an FiO2 ≤ 50% • Mean airway pressure (MAP) < 10 cm H_2O, vent rate ≤ 20 bpm, amplitude < 2X MAP if on HFV • Absence of clinically significant PDA • Hemodynamically stable	**Keep intubated and ventilated until criteria met. Attempt extubation within 24 hours of fulfilling all of the following criteria** • $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples) • FiO2 ≤ 35 with SpO2 > 88% • Mean airway pressure (MAP) < 8 cm H_2O, vent. rate ≤ 20 bpm, amplitude < 2X MAP on HFV • Absence of clinically significant PDA • Hemodynamically stable
Repeated Surf Doses	Subsequent doses may be given at the manufacturer's recommended dose up to a total of 4 doses.	
Intubation	Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery	
CPAP D/C	In room air for at least 1 hour	
CPAP Resumption	At any time	
Duration of Intervention	14 days	14 days

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From: Higgins, Rosemary (NIH/NICHD)
To: "srhintz@stanford.edu"
Subject: Re: SUPPORT MRI Secondary
Date: Wednesday, December 22, 2004 8:22:54 PM

Susan
I am glad you got the message. We have already sent the protocol out to some of the reviewers, so don't worry about an updated version.
Hope your holidays go well. I will be in the office tomorrown until 2PM on monday, dec. 27 and for most of the days on tuesday and wednesday (b) (6) [redacted]). Anyway, I just wanted you to know that the protocol goes to the next step.

Thanks for all of your effortm take care and Happy Holidays!
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Susan Hintz <srhintz@stanford.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Wed Dec 22 20:11:25 2004
Subject: Re: SUPPORT MRI Secondary

Thanks Rose. Our offices are closed this week, but I am still around. In fact, I was working on a "mock" MRI scoring sheet today, which I will send on to our neuroradiologist to see if he has other input. I don't know if you need the "expanded" points for the MRI reading in order to send it on to the outside reviewers? If you want, I can send you an "updated" proposal, which includes the longer list of what we will look for in the MRIs. Just let me know by email, or you can use the hospital direct paging service (call 650-723(b) (6) then enter my page id which is (b) (6) then enter your call back number when prompted).

Thanks

Susan

Susan

I had tried to call earlier, but got a recording - hope the holidays are going well. I have 15 votes in for the secondary study with 14 yeses and one no vote. Therefore, I will send an email to the steering committee letting them know that this is going for outside review.

Here were some comments - 1. I don't think that the rationale is very strong to support the possibility that there could be gross anatomic abnormalities of the brain, visible in infancy, related to either the CPAP or O2 sat interventions.

2. I don't think that the state of the science justifies developing predicition models for neurodevelopmental outcome at 18-22 months. First, I don't think parents are that interested in 18-22 month outcomes. I believe that they are more interested in later outcomes; but this is, of course, an empiric question. Second, I think that this prediction model should have the same justification as aEEG for hypothermia, i.e. to select children for a post-discharge interventional trial.

I will let you kow when I get input from outside review and the advisory board and willwork on potential co-funding in the meantime.

Have a wonderful holiday

Thanks for all your effort!!
Rose

Rosemary D. Higgins, M.D.

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From: Higgins, Rosemary (NIH/NICHD)
To: petrie@rti.org
Subject: MRI
Date: Wednesday, December 22, 2004 4:58:00 PM
Attachments: SC -SUPPORT.Hintz.secondary.rev.doc

Carolyn
Can you send this to the advisor board for input?
Thanks
Rose

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Susan Hintz, Stanford University

NEUROIMAGING AND NEURODEVELOPMENTAL OUTCOME: A SECONDARY TO SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL (SUPPORT)

A. Abstract/Statement of Problem

Cranial ultrasound (US) is currently used for brain imaging in the extremely preterm population, but this modality cannot detect subtle brain injury that may be responsible for later neuromotor and cognitive delay. Magnetic resonance imaging (MRI) can identify brain structural abnormalities and white matter injury better than cranial US. The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) will evaluate if permissive ventilation strategies and lower SpO_2 targets will result in increased rates of survival without bronchopulmonary dysplasia (BPD) and increased rates of survival without retinopathy of prematurity (ROP) among 24-27+6/7 week EGA infants. It is not known whether differing ventilation and oxygenation management approaches could lead to adverse consequences with respect to brain injury. Extremely premature infants are at very high risk for neuromotor and neurodevelopmental impairment, with reported rates of cerebral palsy (CP) ranging from 11-20%, and of severe cognitive delay ranging from 30-60%. Whether MRI and predict neurodevelopmental outcome better than early and/or late cranial US among preterm infants is not yet known, but small preliminary studies are promising. We therefore propose a secondary study to SUPPORT in which specifically timed cranial US (for SUPPORT subjects in all Network centers) and brain MRI (in Network centers able to participate in the brain MRI portion of this proposal) will be obtained. We will use neurodevelopmental follow-up data at 18-22 months corrected age to assess comparative and combined predictive capabilities of these neurodiagnostic modalities ("early" cranial US, "late" cranial US and MRI). We will also test the hypothesis that ventilation and oxygenation strategies in SUPPORT will not be associated with an increase in death or brain injury (Grade 3/4 IVH by cranial US at 7-14 days or 35-42 weeks, abnormal brain MRI at 35-42 weeks). The NICHD Neonatal Research Network is uniquely positioned to embark upon such a project, which would be the first multicenter, prospective study to investigate these important questions.

B. Objective

We propose a secondary, prospective study of cranial US at 7-14 days ("early") and 35-42 weeks postmenstrual age (PMA) ("late") (for SUPPORT subjects in all Network centers), and brain MRI at 35-42 weeks PMA (in centers able to participate in the brain MRI portion of this proposal) among infants enrolled in SUPPORT. We propose to evaluate and compare the capabilities of early and late cranial US and brain MRI to predict neuromotor and neurodevelopmental outcome at 18-22 months corrected age through development of predictive models.

We also propose to determine if ventilatory or oxygen saturation interventions are associated with differences in the outcomes of death or abnormal neuroimaging findings (death/grade 3/4 IVH on "early" US, death/grade 3/4 IVH on "late" US, death/PVL, death/abnormal MRI).

C. Hypotheses

- Multivariate modeling will demonstrate that conventional brain MRI at 35-42 weeks PMA will be superior to cranial US in predicting neurodevelopmental outcome at 18-22 months corrected age.
- There will be insufficient evidence to reject the null hypothesis that no differences exist in frequency of Death/Grade 3/4 IVH or Death/PVL on early or late US between Low and High SpO_2 groups, or between Early CPAP and Control ventilation groups
- There will be insufficient evidence to reject the null hypothesis that the frequency of Death/abnormal findings on conventional brain MRI at 35-42 weeks postmenstrual age (PMA) are not different between Low and High SpO2 groups, or between Early CPAP and Control ventilation groups.

D. Specific Aims

1) To obtain consistently performed, timed and interpreted neuroimaging studies in extremely preterm infants enrolled in SUPPORT:
    a. cranial US at 7-14 days of age (in all centers)
    b. cranial US at 35-42 weeks PMA (in all centers)
    c. MRI at 35-42 weeks PMA (in centers participating in MRI portion of this secondary)
2) To compare early and late US and MRI findings between Low and High SpO_2 groups, and between Early CPAP and Control ventilation groups.
3) To utilize the NICHD Neonatal Research Network follow-up programs to assess neurodevelopmental outcomes at 18-22 months corrected age, as described in SUPPORT.
4) To examine the independent associations of neuroimaging findings with neurodevelopmental outcomes through logistic regression modeling.
    a. Regression models will assess the absolute and relative value of early and late cranial US, and brain MRI, alone and in combination with traditional risk factors, to predict both abnormal and normal neurodevelopmental outcome at 18-22 months.
    b. Through stepwise regression modeling, we will also assess the value of neuroimaging findings, alone and in combination, in predicting neurodevelopmental outcomes over and above the value of early risk factors or early and in-hospital risk factors alone.

E. Background, Significance and Rationale

The importance of an advanced neuroimaging component to SUPPORT:

SUPPORT will be the largest randomized controlled trial of ventilatory and oxygen saturation target management in extremely premature infants to date. Although the primary outcomes for the SUPPORT focus on survival without BPD and survival without ROP, it will be crucial to evaluate the potential impact of study interventions on both neuroimaging findings and neurodevelopmental outcomes. One possible concern could be that lower oxygenation parameters and less aggressive ventilatory management may be associated with a higher incidence of brain injury. This position might be extrapolated from earlier observations in preterm infants (1,2), and from studies of near-term and term hypoxic brain injury.

Other investigations suggest that more aggressive ventilation strategies leading to hypocapnia may place the premature infant at higher risk for reduced cerebral blood flow (CBF) and subsequent white matter injury. The CBF-carbon dioxide reactivity observed in adult animals may be blunted or incomplete in newborn and preterm animals (3,4). Nevertheless, several clinical case series of preterm infants have demonstrated strong associations of hypocapnia with significant abnormal findings on brain imaging and with adverse neurodevelopmental outcome (5-8), although other important risk factors were also identified.

At the very least, neuroimaging abnormalities in preterm infants are likely to be the result of a multifactorial process. Emerging evidence points to the unique vulnerability of the preterm infant brain in several respects. Low blood flow to the cerebral white matter and impaired cerebrovascular autoregulation in premature infants (9-11) may make subtle brain ischemic injury more likely. Coupled with this tendency to ischemic injury, is the vulnerability of developing oligodendroglial cells to damage (see below). Finally, it is possible that effects of exposure to *in utero* infection, frequently suspected in extremely preterm infants, may potentiate brain cellular injury caused by mild to moderate ischemia (12,13).

Summary: Given the interventions to be undertaken in SUPPORT, and the complexity and multifactorial nature of the development of white matter injury in the premature brain, advanced neuroimaging could be a critical component to the trial. This proposed secondary to SUPPORT would provide important additional information to investigators with respect to the impact of respiratory management on subtle brain injury.

The need to investigate emerging brain imaging modalities:

Premature infants are at high risk for neuromotor and neurodevelopmental impairment. Recent reported rates of cerebral palsy (CP) at 18-24 months corrected age range from 11-20%, and of cognitive delay range from 30-60% for the extremely low birth weight (ELBW) population (14-16). Yet, despite numerous investigations, the complete explanation of these impairments remains unclear. Correlation of specific neonatal factors, particularly neuroimaging findings, with adverse neuromotor and neurodevelopmental outcomes are frequently demonstrated. Many studies have emphasized the association of cranial US abnormalities including intraventricular hemorrhage (IVH) grades 3 and 4, periventricular leukomalacia (PVL) and ventricular dilatation with subsequent neurologic and cognitive impairment (14-20). Most investigators have found abnormalities on cranial US to be an independent risk factor for neuromotor abnormalities, but not necessarily for cognitive impairment.

But, the finding of severe cranial US abnormalities is not uniformly predictive of adverse neuromotor outcome in the premature population. In a study of perinatal correlates of neurologic impairment at 18-22 months corrected age among VLBW infants (20), only 52% of the infants with CP on follow-up had had severe cranial US abnormalities. This finding was in contrast to a 12% rate of severe cranial US abnormalities among matched controls without CP. In a neurodevelopmental follow-up study of ELBW infants in a multicenter, double masked, randomized controlled trial of indomethacin prophylaxis in preterms (TIPP), rates of survival without neurosensory impairment were found to be similar between treatment groups although incidence of

grade 3 or 4 IVH on cranial US had been significantly reduced by treatment with indomethacin (21).

Smaller studies have investigated the capabilities of cranial US at term to predict CP among preterm infants, revealing that the sensitivity of this diagnostic tool is only approximately 60% (22,23). Other reports have indicated that cystic PVL may be detected in infants without previous cranial US abnormalities at several months of age (24-26). These studies suggest that only certain types of brain injury may be detectable with cranial US, and that timing of studies may be crucial. Furthermore, the radiologic changes associated with PVL may be visible by US only at a particular point in time; if cysts do not form as a result of injury leading to PVL, it may not be visible by US. Thus, injury could have occurred but would not be detected by US.

Summary: Cranial US, the imaging modality currently considered to be standard of care, may not be sensitive enough to detect brain injury that is responsible for later neuromotor or neurodevelopmental delay among ELBW infants.

MRI compared with cranial US to assess of brain injury and predict neurologic outcome

MRI provides a more complete and anatomically detailed evaluation of the neonatal brain. Several studies have compared the relative capabilities of US with MRI to detect brain injury among preterm infants in the newborn period. These reports concluded that MRI detects white matter injury better than HUS (27-29), and provides additional information regarding hemorrhage and cystic changes not noted by cranial US. Childs, et. al. assessed MRI and serial cranial US in both preterm and term infants, and concluded that MRI was more sensitive in identifying periventricular white matter lesions (30). However, neurodevelopmental outcome of the infants in those studies were not reported.

Few studies have compared MRI with cranial US in terms of their capabilities to predict neurodevelopmental outcome among premature infants; those are small, primarily single-center efforts. Furthermore, due to variability of timing, of imaging, and differences in MRI scoring and interpretation, the studies are difficult to compare. Valkama, et. al. (31) assessed MRI compared with cranial US performed at term in 51 VLBW, preterm infants (<34 weeks). Twelve infants were diagnosed with CP at 18 months corrected age. MRI parenchymal lesions predicted CP with 100% sensitivity and 79% specificity whereas US at term predicted CP with 67% sensitivity and 85% specificity. The authors concluded that MRI was the more reliable methodology. Stanford University researchers (see below "Preliminary Studies and Results") have completed a prospective study of neuroimaging among VLBW, preterm infants with neurodevelopmental follow-up at 18-22 months and 30 months corrected age (32). MRI at term predicted CP with superior sensitivity and positive predictive value compared with early cranial US.

Other studies have suggested the potential prognostic advantages of MRI compared with cranial US. Roelant-van Rijn and colleagues (33) studied 61 preterm infants with cranial US, and MRI within the first weeks of age and/or at term. MRI at term was found to be helpful in delineating internal capsule abnormalities, considered to be useful in predicting later hemiplegia. Other preliminary reports include that of Austin, et. al. (34) in which 93 VLBW infants evaluated with brain MRI at term underwent

neurodevelopmental assessments at one year corrected age. White matter injury on MRI at term was correlated with neuromotor abnormalities such as hypertonicity, hypotonicity, and motor delay. In a very small group of premature infants <36 weeks, Miller, et. al. (35) showed that cerebellar hemorrhages detected by MRI, even if not associated with white matter injury, appeared to be associated with adverse neurodevelopmental outcome at 12 months.

There are potential criticisms to these studies. In most cases, MRI was compared with only "late" cranial US or only "early" US; a more complete comparison would include both early and late cranial US, demonstrating that the design of neuroimaging collection strategies in prospective studies is crucial. Many studies focus narrowly on neuromotor outcome, specifically the prevalence of CP, as outcome variables. A broader neurodevelopmental assessment and comparison is warranted. Finally, all studies of MRI findings and correlation with neurodevelopmental outcomes in preterm infants thus far are small; it is therefore not possible to draw powerful conclusions, especially with regard to ELBW patients. In fact, the recently published "Practice Parameter: Neuroimaging of the Neonate" (36) failed to definitively recommend routine MRI for VLBW preterm infants in large part due to the lack of follow-up studies. But, many of the reports reviewed above were not available during the development of the "Practice Parameter".

Summary: Studies to date suggest that MRI may be a more powerful tool in predicting adverse neuromotor outcome among preterm infants. However, timing of studies vary between published reports, and very few prospective neurodevelopmental follow-up investigations have been undertaken to assess the comparative prognostic capabilities of these neuroimaging techniques for neuromotor and cognitive outcomes.

The importance of subtle white matter injury

Periventricular leukomalacia (PVL) has been categorized as "focal" and "diffuse" (37,38). Focal PVL has been described as the result of severe ischemic-necrotic injury and is located deep in the white matter. This type of injury may lead to the development of cystic changes or significant findings that can be detected by cranial US or conventional MRI. Diffuse PVL is thought to be the result of less severe injury, diffusely located in the white matter. The mechanism of diffuse PVL may be multifactorial, including: 1) mild to moderate ischemia due to decreases in cerebral blood flow consistent with impaired autoregulation, 2) vulnerability of immature oligodendroglial cells to ischemic injury and damage by chemical mediators, and 3) oligodendroglial cell susceptibility to injury and death after intraventricular hemorrhage due to creation of oxygen free radicals. The sensitivity of the immature oligodendroglial cells to cytokine-induced injury may help to provide a pathophysiologic explanation to the observations of increased CP rates among infants born to mothers with chorioamnionitis, and among infants with early sepsis.

Diffuse PVL may be a clinically important and prevalent white matter injury in the preterm infant. Yet, diffuse PVL is unlikely to be seen by cranial US. Diffuse PVL may also be challenging to detect reliably on conventional MRI. However, in a study by Counsell et. al. (39), diffuse excessive high signal intensity (DEHSI) in the white matter of preterm infants at near-term was associated with higher apparent diffusion coefficient

values on diffusion weighted MRI. This finding suggested that subtle injury, causing changes in cellular differentiation and probable preferential death of preoligodendrocytes, resulting in diffuse PVL (40), may be structurally visible in the form of DEHSI. The developmental significance for the preterm infant is not known. It is also important to note that not all subtle white matter injury is likely to be detectable even by MRI.

Summary: IVH and focal cystic PVL are detectable by conventional MRI or even cranial US. However, more subtle factors and injuries may lead to oligodendroglial cell death and diffuse PVL. Diffuse PVL is not likely to be detected by cranial US, but might be detected by MRI. Such injury may have a substantial impact on normal white matter development and neuromotor outcome in the preterm infant; however, this question has been poorly studied in a large-scale, prospective manner.

Preliminary Studies and Results

A coordinated effort among neonatologists, radiologists, engineers, technicians and developmentalists has been in place at Lucile Salter Packard Children's Hospital and the Lucas Center for Nuclear Magnetic Resonance at Stanford University since the late 1990's. The objective of this group has been to combine the talents and expertise from various fields of science to investigate novel, potentially clinically relevant neuroimaging approaches in term and preterm infants. As a result, a strong infrastructure exists to allow for the development and implementation of further prospective studies and trials of MRI in the neonatal population.

Cranial US vs. conventional MRI for prediction of CP in VLBW infants: Infants of <1250 grams and <30 weeks EGA were enrolled a prospective observational study of the capabilities of early cranial US compared with conventional MRI at near-term to predict CP at 18-22 months corrected age, and 30 months (32). Cranial US was obtained twice during the first two weeks of life, and the most abnormal findings were used for analysis. Conventional MRI and cranial US were scored with respect to size of hemorrhage, parenchymal involvement, and ventricular dilitation. 62 infants participated in the study, with one excluded from analysis due to a later diagnosis of muscular dystrophy. The sensitivity and specificity of near-term MRI for predicting CP at 18-22 months were 71% and 91% respectively. The sensitivity of MRI for predicting CP at 30 months of age increased to 86% with the specificity remaining high at 89%. Although the specificity was comparable to MRI, the sensitivity of US to predict CP was only 29% at 18-22 months and 43% at 30 months. The positive predictive value of US was 22% at 18-22 months and 33% at 30 months.

This study, one of the largest prospective comparative neuroimaging studies of VLBW infants and neurodevelopmental outcome, supports the suggestion that conventional MRI may be superior to cranial US with respect to prediction of neuromotor abnormalities. There are limitations to this study, however. Comparison cranial US were performed early in the hospital course (<2 weeks), and no US contemporaneous with the MRI were routinely obtained. Recent studies by other investigators have also determined that, among VLBW infants, early cranial US poorly predicts non-cystic white matter injury on MRI at term (41). Also, previous reports by

Valkama, et. al. (31) suggest that cranial US at term was a substantially less sensitive predictor of CP than MRI at term. Nevertheless, a thorough comparison would include early and later cranial US determinations to evaluate the potential combined prognostic power of early and late cranial US compared with MRI at term. In addition, this study was significantly limited by small sample size, with only seven infants diagnosed with CP on neurodevelopmental follow-up. Sample size considerations also restricted possibilities for multivariate modeling of outcomes, and meaningful analysis of Bayley Scales of Infant Development II scores. All of these limitations could be addressed in the proposed prospective multicenter study.

F. Research Design and Methods

1. Study Design: This proposed secondary to SUPPORT is a prospective study of traditional (cranial US at 7-14 days and 35-42 weeks PMA) and advanced (MRI at 35-42 weeks PMA) neuroimaging with respect to SUPPORT randomized ventilation and oxygen saturation interventions. The capabilities of these neuroimaging modalities to predict neurodevelopmental outcome at 18-22 months corrected age will also be assessed. **It is proposed that all subjects enrolled in SUPPORT should be able to participate in the cranial US portion of this proposal. It is understood that not all sites will be able to participate in the MRI portion of the proposed secondary. (SEE 3.b "Neuroimaging studies" below)**

Perinatal, demographic and neonatal data will be collected as part of the ongoing NICHD Neonatal Research Network Survey of Morbidity and Mortality Among VLBW Infants (401-1500g) for the purposes of the study. Cranial US will be obtained at 7-14 days and at 35-42 weeks PMA. *Clinical* interpretation of cranial US will continue to be performed at individual Network sites, but for purposes of research outcomes, cranial US should ideally be interpreted by central readers. Brain MRI will be obtained at 35-42 weeks PMA; MRI will be interpreted by a central reader(s) for purposes of research outcomes, but clinical interpretation will be performed at individual Network sites. Detailed neuromotor and neurodevelopmental examinations will be undertaken at 18-22 months corrected age as part of the NICHD Cooperative Multicenter Network of Neonatal Intensive Care Units: Follow-Up of ELBW Infants (401-1000g), and per SUPPORT protocol.

Statistical analysis will include bivariate analyses, and logistic regression modeling to 1) assess the association of SUPPORT ventilation and oxygenation randomized treatment groups with neuroimaging, 2) evaluate the strength of independent associations of specific neuroimaging findings with neurodevelopmental outcomes and 3) develop predictive models.

2. Study Population

Inclusion Criteria

- Enrolled in the NICHD Neonatal Research Network SUPPORT study
- **FOR ALL CENTERS:** Cranial ultrasound can be obtained at 7-14 days of age and at 35-42 weeks PMA
- **FOR CENTERS PARTICIPATING IN BRAIN MRI PORTION OF PROPOSED SECONDARY:** Brain MRI can be obtained per study specifications (see Appendix D) at 35-42 weeks PMA.

- If MRI cannot be performed by 42 weeks due to subject clinical condition (See Appendix B), the "late" cranial US would also be delayed such that the cranial US is within 7 days of the brain MRI.

Exclusion Criteria

- **FOR ALL CENTERS:** Patient is likely to be discharged or transferred by 35 weeks PMA to a facility where cranial US is NOT available.
- **FOR CENTERS PARTICIPATING IN BRAIN MRI PORTION OF PROPOSED SECONDARY:** Patient is likely to be discharged or transferred by 35 weeks PMA to a facility where cranial MRI is not available.
- Patient unlikely or family unwilling to participate in neurodevelopmental assessment at 18-22 month corrected age
- Presence of known or suspected congenital anomalies including:
  - ➤ Chromosomal anomalies
  - ➤ Complex congenital heart disease (PDA, small muscular VSD or PFO are NOT considered to be congenital heart disease for the purposes of this study)
  - ➤ Congenital infection (TORCH, untreated maternal HIV, syphilis)
- Lack of informed consent

Enrollment of Subjects

Screening: Each center will be responsible for devising a screening strategy to identify all potential participants using the study inclusion and exclusion criteria. Screening and identification of patients should take place by 14 days of age since the "early cranial US" must be performed at 7-14 days.

Informed consent: Each participating center will follow procedures for developing informed consents as set out by the local Institutional Review Board (IRB). It is expected that the parents of all eligible infants will be approached to participate in this prospective study, and informed consent must be obtained by the individual center.

Eligible infants not enrolled: The reasons for non-enrollment will be documented. Short- and long-term outcomes of eligible infants not enrolled in this study will be documented as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality in VLBW Infants (Generic Data Base (GDB)) and, if enrolled, as part of the ongoing NICHD Neonatal Research Network ELBW neurodevelopmental follow-up study.

No MRI obtained for infants enrolled in the MRI portion of the study: An important objective of the proposed study requires acquisition of MRI at 35-42 weeks PMA; it is important that each participating center make this a priority. However, it is understood that if the patient is deemed medically unstable (Appendix B) during the entire 35-42 week PMA period, an MRI will not be obtained during that period. If the patient is medical unstable, MRI MAY BE DELAYED beyond 42 weeks, however LATE CRANIAL US SHOULD ALSO BE DELAYED in that case, such that the studies are still obtained within 7 days of each other.

3. BASELINE DATA, NEUROIMAGING, NEURODEVELOPMENTAL FOLLOW-UP

a. Baseline Data: Perinatal, demographic and in-hospital variables

i. INTRODUCTION AND FEASIBILITY: This secondary protocol will not require substantial data collection in addition to that already in place at participating centers; nor

will it mandate patient management. The majority of data collection instruments will be those already in routine use in the participating centers through the NICHD Neonatal Research Network Survey of Morbidity and Mortality in VLBW Infants. These data are obtained through the use of "Generic Data Base forms" which allows for consistent accrual of demographic, perinatal and neonatal variables among this high-risk population.
ii. METHODS: Research nurses at participating centers will collect data using the standardized Generic Data Base Forms. Additional queries will attempt to delineate the potential independent contribution of hypotension and hypocarbia, purported to be causes of cerebral hypoperfusion (42-46) leading to diffuse or focal neonatal brain injury, to abnormalities on MRI. These questions will be coordinated with the SUPPORT protocol subcommittee and focus on 1) need for pressors and 2) the degree of hypocarbia experienced

Since these infants will be participating in the SUPPORT trial, information regarding ventilation strategy and oxygen saturation randomization arms will also be available.

b) Neuroimaging studies
i. INTRODUCTION AND FEASIBILITY: Changes in the approach to neuroimaging may be required for implementation of this research protocol at participating centers. The extent of the changes will depend upon the procedures already in place at each individual center, and the level of participation (i.e., cranial US portion ONLY vs. cranial US and brain MRI portions of this secondary). In addition, budgetary constraints may limit participation.

CRANIAL US: Within the Neonatal Research Network, cranial US should already routinely be performed in ELBW infants 7-14 days of age window, and should also be performed at near-term among sites that are not performing MRI as the near-term brain imaging modality. The most recent results (November 2004) of the Preterm Infant Neuroimaging Questionnaire indicate that all but one Network center reported that cranial US are routinely obtained at 7-14 days among infants <28 weeks EGA. The one remaining center reported obtaining cranial US earlier than 7 days. Therefore, for the cranial US portion of this proposed secondary, **no additional imaging would be required for sites using only US as the routine neuroimaging modality.** For the purposes of this study however, central neuroimaging readers should ideally be used for both early and late cranial US since disparate interpretations of would potentially complicate analysis. Additional costs would therefore be incurred with respect to coordinator time (tracking, gathering, sending studies) and central reading.

BRAIN MRI: The most recent results (November 2004) of the Preterm Infant Neuroimaging Questionnaire reveal that two Network sites currently use brain MRI as the routine near-term VLBW imaging modality, with one additional site planning to implement routine MRI, and 4 other sites "considering" a change to MRI. Therefore, for those sites utilizing MRI as the routine near-term neuroimaging modality, **only one additional study, a cranial US at near-term, would be required.** In addition to the cost of the additional imaging study, costs would be incurred as noted above with respect to coordinator time and central reading.

WHICH CENTERS WILL PARTICIPATE IN THE BRAIN MRI PORTION OF THIS PROPOSED SECONDARY? Network centers with devices capable of performing neonatal conventional brain MRI (4 mm slice) could participate in the MRI portion of this proposed study. **Sites not performing brain MRI as the routine near-term neuroimaging study MAY be able to participate in the Brain MRI portion of this secondary. However, due to budgetary considerations, it is possible that implementation of this proposed secondary may be limited only to selected Network sites.** The most conservative approach would be that only those sites in which MRI is currently, or will soon be, implementing routine near-term MRI will participate in this proposed secondary.

ii. METHODS:

1) "Early cranial ultrasound": A cranial ultrasound will be obtained at 7-14 days of age. If more than one cranial ultrasound is obtained during that time period, the ultrasound obtained closest to 14 days will be used. Results will be interpreted as indicated in the Manual of Operations (See Appendix C), and reported in the NG03 form, but central readers will formally interpret ultrasounds.

Although not currently *required* within the parameters of the NICHD Neonatal Network VLBW Registry, recent ELBW neurodevelopmental follow-up studies from the NICHD Neonatal Research Network reveal that virtually all of these extremely high risk infants surviving to the 18-22 month visit have had at least one cranial US early in the course of their hospitalization. Furthermore, the "Practice Parameter" for neuroimaging in the neonate recommends *screening cranial US should be performed on all infants with EGA of <30 weeks at 7-14 days of age* (36); it is likely that Network centers have already implemented this practice to patient care protocols.

2) "Late cranial ultrasound": A cranial ultrasound will be obtained at 35-42 weeks PMA, and within 7 days of brain MRI. All late cranial US will be reported in the NG03 form as indicated in the Manual of Operations (See Appendix C), and will be interpreted by central readers.

Late cranial US is not currently required in the Network paradigm. However, the "Practice Parameter" as referred to above (36) recommends that *cranial US should be optimally repeated at 36-40 weeks' postmenstrual age*, so it is likely that Network sites have implemented this routine imaging.

FOR CENTERS PARTICIPATING IN THE BRAIN MRI PORTION OF THE PROPOSED STUDY:

3) Brain MRI: A brain MRI will be obtained at 35-42 weeks PMA, and within 7 days of the "late cranial ultrasound". Images will be acquired as described in Appendix A. Conventional MRI images will be transferred to Stanford University for interpretation and scoring by central pediatric neuroradiologist reader(s) (Patrick Barnes, M.D., and others as suggested by the Steering Committee) who will be masked to any unique patient identifiers and to patient history and outcome. Dr. Barnes is a highly regarded, widely published pediatric neuroradiologist with extensive experience in the field of MRI, MR spectroscopy, diffusion weighted and diffusion tensor imaging. In addition to his dedicated work at Stanford University, Dr. Barnes has also collaborated with researchers such as TE Inder, PS Huppi and JJ Volpe. Dr. Barnes is an expert in the timing of fetal and neonatal brain injury using methods such as MRI and MRS.

MRI interpretation and data access: Conventional MRI images will be interpreted and scored by a central neuroradiology reader (Appendix C). The central reader(s) will be responsible for completion of data forms and data transfer to the Network Data Center. Each participating center is expected to counsel families with regard to MRI findings on the basis of its own neuroradiologist's interpretation of the images.

Sedation issues: MRI studies are performed without sedation at Stanford University. Patients are imaged following a feeding, ear plugs (MiniMuffs, Natus) are used to reduce the noise by up to 50% and patients are bundled to preserve warmth, maintain sleep and reduce patient motion. Of the 14 sites that responded to an earlier NICHD Neonatal Research Network Brain Imaging Survey (Dr. Seetha Shankaran), five indicated that they already use sedation for MRI. Another six sites indicated that sedation is used if clinically necessary. One site responded that sedation is not used. Responses from two centers were not clear. At Stanford, the approach of "feeding and swaddling" has yielded successful conventional MRI imaging with excellent quality in almost all cases. Sedation, if needed, would clearly increase the likelihood of obtaining a high quality scan. Network centers in which sedation is standard of care, and MRI is routinely performed, should certainly be able to continue their current approach. Although several of the sites have already indicated that sedation is used routinely, it is appreciated that the use of sedation in the context of a research protocol may make IRB approval more difficult. One possible solution for centers with such challenges would be to present two consent forms: the first for participation in the study itself, indicating that "feeding and swaddling" methods would be tried; the second, for consent to use sedation if this conservative approach were not successful, or if it is considered medically inadvisable to implement the "feeding and swaddling" approach (i.e., severe reflux). Clearly there are differing approaches to sedation for MRI studies, thus the issue of sedation will be left to the individual investigators at each Network site.

c) Neurodevelopmental Follow-up

i. INTRODUCTION AND FEASIBILITY: Neurodevelopmental follow-up for ELBW infants is already a focused objective within the NICHD Neonatal Research Network; all Network centers have complete neurodevelopmental assessment teams and patient tracking infrastructure in place. In addition, neurodevelopmental follow-up is already a part of SUPPORT protocol.

ii. METHODS: Follow-up visit will be conducted at 18-22 months corrected age as described in the "NICHD Neonatal Research Network ELBW Follow-Up Study Manual of Operations" (see Appendix C). An exam for neurological exam for cerebral palsy will be performed. The Bayley Scales of Infant Development (Bayley N. Bayley Scales of Infant Development-II. San Antonio, TX: Psychological Corporation; 1993) will be administered by a Bayley Examiner certified for the Follow-Up Study. In addition to neurodevelopmental assessments, information regarding socioeconomic status, level of education of the primary caregiver, and marital status is routinely obtained at the 18-22 month visit.

4. STATISTICAL CONSIDERATIONS

Outcomes:

Primary outcomes considered will include

- Death/Grade 3/4 IVH on 7-14 day cranial US
- Death/Grade 3/4 IVH on 35-42 week cranial US
- Death/PVL on 35-42 week cranial US
- Death/abnormal MRI at 35-42 weeks

Secondary outcomes will include
- cerebral palsy
- BSID MDI<70
- BSID PDI<70
- Neurodevelopmental impairment (NDI) defined as any of the following: deafness, blindness, moderate-severe cerebral palsy, or BSID II MDI or PDI score <70.

Bivariate analyses: Analyses of frequency of primary outcomes with respect to SUPPORT treatment groups will be undertaken. Comparisons will be made between ventilation strategy groups (Early CPAP and Control groups) within each randomized oxygenation group, and between oxygenation strategy groups (Low and High SpO2) within each randomized ventilation group. Continuous measures will be compared using the Student t-test and ANOVA where appropriate, and Chi-square analysis will be used to compare categorical data. These analyses would also adjust for the clustering effect introduced by randomizing by week of study.

Sample size and power issues:
Overall GDB and follow-up patient numbers: For year 2003, 1468 infants 24+0 to 27+6 weeks EGA were enrolled in GDB. Of those, 1249 survived to >7 days and 1209 survived to >=14 days. 1027 patients survived to hospital discharge. In year 2003, a total of 725 former 24+0 to 27+6 week EGA patients completed neurodevelopmental assessment at 18-22 months corrected age.
Frequency of neuroimaging outcomes:
Ultrasound: For year 2003, among infants 24+0 to 27+6 weeks EGA surviving to >=14 days, the frequency of Grade 3/4 IVH on cranial US was 20.3%; for those surviving to discharge it was 18.6%. The frequency of PVL among those surviving to discharge was 3.9%.
MRI: "Abnormal" conventional MRI results among preterm infants at near term are much more difficult to quantify. This is due both to a paucity of available data in the literature, and disparate methods of reporting and scoring "abnormalities" on brain MRI among preterm infants. Two recent studies have attempted to estimate the frequency of white matter signal abnormality, as well as other abnormal findings. Inder and colleagues (47) reported on findings of brain MRI performed at term equivalent age in 100 infants of 23-32 weeks EGA. Only 36/100 were considered to have no white matter signal abnormality, whereas 16/100 had extensive severe white matter signal abnormality. Cortical gray matter abnormalities were rare, with 96/100 patients categorized as normal. Lateral ventricle size was normal in only 40/100. Miller, et. al. (48) reported on MRI findings of 32 consecutive preterm infants, but imaging was performed at earlier postconceptual ages. In addition, previous studies by Maalouf (27) found that 12/19 (63%) preterm infants studied by MRI at 38-44 weeks PCA had abnormal white matter signal, but of those only 7 were moderately to severely abnormal (37%). Childs (30)

found 29 of 105 preterm infants (<37 weeks) had abnormal periventricular white matter on MRI, and an additional 5 infants with other abnormalities (32% abnormal). However, the age at the time of MRI in that study ranged from 1-42 days, and PCA at time of scan was not reported. Counsell, et. al. found that, among preterm infants at near term, 34 of 50 had "overt" white matter abnormality or diffuse excessive high signal intensity white matter abnormalities (68% abnormal) (39). In summary then, the frequency of "abnormal" brain MRI in preterm infants ranges from 32-68%. One projected benefit from this proposed secondary study, in fact, would be that the frequency of specific MRI abnormalities in a large premature group could be better clarified and described. For the purposes of sample size and power calculations for this proposal, a conservative estimate of 40% white matter abnormality by MRI at 35-42 weeks will be used.

Thus, the following are the estimated rates for four major outcomes examined in this proposal:

I) Death/Grade 3/4 IVH (14 day)	34.2%
II) Death/Grade 3/4 IVH (at d/c, an estimate of 35-42 weeks)	42.9%
III) Death/PVL (at d/c, an estimate of 35-42 weeks)	32.8%
IV) Death/MRI abnormality	58%

Sample size and detectable difference estimates if all centers could participate in both cranial US and brain MRI portions of study:
The revised projected sample size required for SUPPORT is 1310 patients (or 328 patients per each of 4 treatment groups). It is unlikely that all centers could participate in both cranial US and Brain MRI portions of this proposed study. But, if one used an estimate of 80% enrollment in the proposed study, 1048 patients would be enrolled. This would provide 262 patients in each for 4 groups, such that bivariate comparisons will be made between ventilation strategy groups (Early CPAP vs. Control ventilation groups) within each randomized oxygenation strategy, and between oxygenation strategy groups (Low vs. High SpO2) within each randomized ventilation strategy.

Note that 80% enrollment should be considered a conservative estimate for the cranial US portion of this study – virtually all SUPPORT subjects should be able to participate in the cranial US portion of this study.

Thus, for the outcome of Death/Grade 3/4 IVH (14 day), using an expected prevalence rate of 34.2% (see above), a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	33.9% = 34.2% to 22.6%
% increase from expected	35.9% = 34.2% to 46.4%

For the outcome of Death/Grade 3/4 IVH (35-42 week), using an expected prevalence rate of 42.9%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	28.4% = 42.9% to 30.7%

% increase from expected	29.4% = 42.9% to 55.4%

For the outcome of Death/PVL by cranial US (35-42 week), using an expected prevalence rate of 32.8%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	34.4% = 32.8% to 21.5%
% increase from expected	36.9% = 32.8% to 44.9%

As noted above, it is unlikely that 80% enrollment could be achieved for the Brain MRI portion of this study. However, if this were to be possible, the following would apply:

For the outcome of Death/MRI abnormality (35-42 week), using an expected prevalence rate of 58%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	21.6% = 58% to 45.5%
% increase from expected	20.7% = 58% to 70%

The detectable differences were also calculated for an alpha of 0.01 to adjust for the four primary outcomes. Thus,

For the outcome of Death/Grade 3/4 IVH (14 day), using an expected prevalence rate of 34.2% (see above), a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	40% = 34.2% to 20.5%
% increase from expected	43.2% = 34.2% to 49%

For the outcome of Death/Grade 3/4 IVH (35-42 week), using an expected prevalence rate of 42.9%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	33.6% = 42.9% to 28.5%
% increase from expected	35.2% = 42.9% to 58%

For the outcome of Death/PVL by cranial US (35-42 week), using an expected prevalence rate of 32.8%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	40.2% = 32.8% to 19.6%
% increase from expected	42.7% = 32.8% to 46.8%

For the outcome of Death/MRI abnormality (35-42 week), using an expected prevalence rate of 58%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	25.8% = 58% to 43%
% increase from expected	24.8% = 58% to 72.4%

If MRI could not be performed in all sites due to budgetary constraints, clearly differences between groups with respect to the outcome of Death/MRI abnormality would need to be larger in order to detect. If the number of patients involved in the MRI portion of the proposed study were reduced by one-half (to 524), then the sample size per group would drop to 131. In that case:

For the outcome of Death/MRI abnormality (35-42 weeks), using an expected prevalence rate of 58%, a projected sample size of 131 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	37% = 58% to 36.5%
% increase from expected	35.5% = 58% to 78.6%

However, recall that the estimate of 40% white matter abnormality on MRI among preterm infants at term is conservative, thus the estimate of 58% for the outcome of Death/MRI abnormality may also be conservative.

Regression Analyses: In addition to bivariate analyses, regression analyses will be undertaken to attempt to adjust for confounding variables in comparisons of treatment groups with respect to neuroimaging findings. The independent association of ventilation strategy will be determined for each neuroimaging outcome (Grade 3/4 IVH at 7-14 days, 35-42 weeks, PVL at 35-42 weeks, MRI abnormality), adjusting for gestational age, weight, and oxygenation strategy. Similarly, the independent association of oxygenation strategy will be determined for each neuroimaging outcome (Grade 3/4 IVH at 7-14 days, 35-42 weeks, PVL at 35-42 weeks, MRI abnormality), adjusting for gestational age, weight, and ventilation strategy.
Neurodevelopmental Outcomes Logistic Regression Models: We propose a novel approach to the comparison of neuroimaging modalities with respect to neurodevelopmental outcomes, that of logistic regression modeling. Numerous neurodevelopmental outcomes studies have used this approach, however previous studies of brain MRI in the premature infant have lacked the sample size to implement this statistical technique. Models will be developed to include perinatal, demographic, neonatal and socioeconomic factors pertinent to neurodevelopmental outcome as demonstrated in previous reports (14,15) and the univariate and multivariate analyses carried out. Neuroimaging study results (cranial US at 7-14 days, cranial US at 35-42 weeks PMA, and brain MRI at 35-42 weeks) will be added to the model individually and in combination, to determine the adjusted risk for adverse outcome that each imparts, and to ascertain if any two abnormal studies (i.e., early cranial US and MRI, or early and late US) are materially more predictive of neurodevelopmental impairment than any single abnormal study. Ventilatory strategy and oxygen saturation strategy will also be available as crucial neonatal factors that may impact on outcome.

Predictive modeling of outcome: Challenges to the development of a predictive model include the need for both a "model development" data set and a "model validation" data set. Possible solutions to this challenge include splitting the proposed study data set in half, thus creating a development and validation set; or by employing a so-called "boot-strapping" technique by which multiple random samples of the data set are used for calculating confidence intervals for predictions (49). Further analysis will be required to determine the best strategy for predictive modeling in the proposed study.

Further Statistical considerations: Development and comparison of predictive models:

I. Initial model development, the models and their variables.

The sample will be randomly split into a development dataset with 50% of cases and 50% of controls and a test dataset with 50% of cases and 50% of controls. Several models will be developed of which the following are projected to be central models; however, additional models may also be developed:

1. "Classic" risk model, including traditional factors (i.e., gestational age, birth weight, gender, race, maternal education, etc.) as well as "worst" early cranial US
2. Late cranial US model
3. Conventional MRI model

For each model, the number of categorical variables will be restricted to 5 – 10 observations per category cell. When candidate variables exceed this ratio, the best set of significant predictor variables will be chosen by forward selection. In this case, at each step the variable with the most significant effect will be identified and added to the model. The same dataset will be used for the development of each model.

II. Model calibration and goodness-of-fit

Each model will be calibrated using Pearson chi-square, likelihood ratio chi-square, and Hosmer and Lemeshow statistic.

III. Model discrimination and predictive ability

Sensitivity (true positive rate) and specificity (true negative rate) of the models to predict outcome will be evaluated. The receiver-operator curve (ROC) will be used to display model discrimination by plotting sensitivity against specificity. The predictive abilities of the models will be compared using area under the curve (AUC) analyses (Hanley JA and McNeil BJ, *Radiology* 1982)

IV. Multidimensional model.

Finally, we will attempt to build a model that combines the most significant factors from cranial US and MRI models and compare to the above models.

APPENDICES

Appendix A: Magnetic resonance imaging requirements and image acquisition

Conventional MRI: Network centers that have any "type" of device (i.e., GE, Philips, Siemens, etc.) capable of performing standardized conventional neonatal brain MRI

sequences with 4 mm contiguous slices (0mm gap) will be able to participate. All examinations will include conventional fast spin echo (FSE) T1-weighted and T2-weighted sequences as well as fluid attenuated inversion recovery (FLAIR) and gradient echo (GRE) sequences.

Appendix B: Medical instability at 35-42 week PMA MRI

For "medical instability" to be considered the cause of non-acquisition of MRI, one of the following conditions should exist during the entire 35-42 week PMA MRI imaging window:

- The patient is intubated.
- The patient is considered by the attending neonatologist to be critically unstable such that transport to the radiology suite would be unsafe.

Appendix C: Neuroimaging and neuromotor evaluation

Ultrasound scoring instruments will be modified from the PiNO central reader forms, but will include reference to the following findings, and will be delineated as unilateral or bilateral:

Early Cranial Ultrasound:

- Grade I: blood/echodensity in the germinal matrix/subependymal area
- Grade II: blood/echodensity in the lateral ventricle without distention
- Grade III: blood/echodensity in the lateral ventricle with distention
- Grade IV: blood/echodensity in the parenchyma
- Periventricular leukomalacia
- Cystic periventricular leukomalacia

Late Cranial Ultrasound

- See above
- Porencephalic cystic changes
- Ventriculomegaly
- Presence of shunt

Adjustments and amendments to the following MRI interpretation scheme may be made after further discussion and input from members of the Steering Committee and SUPPORT Subcommittee.

Conventional MRI interpretation:

- C1 = normal
- C2 = minimal subependymal hemorrhage or mineralization with no or mild ventriculomegaly
- C3 = moderate to severe ventriculomegaly
- C4 = parenchymal abnormality
- C5 = periventricular cystic abnormality
- C6 = white matter signal abnormality
- C7 = increased extra-axial fluid
- C8 = cerebellar hemorrhage or mineralization
- C9 = diffuse excessive high intensity signal

Cerebral Palsy ("Neonatal Research Network Follow-Up Study Manual of Operations")
Cerebral palsy at 18-22 months will be diagnosed if definite findings are encountered on exam in any two of the following three areas:

1) Delay in motor milestones – determined using the motor quotient as described in the Manual of Operations.
2) Abnormalities observed in the classical neuromotor exam, which includes measurement of tone, deep tendon reflexes, coordination and movement (not including eye movement). Any one abnormality, except for isolated low tone or toe walking is sufficient.
3) Aberrations in primitive reflexes and postural reactions – any aberration is sufficient.

Cerebral palsy will be further categorized by type and severity, as described in the Manual of Operations.

Human Subjects

1. Risks to the subjects:

a) Human Subjects Involvement and Characteristics: Infants enrolled in the NICHD Neonatal Research Network SUPPORT trial will be recruited. Inclusion and Exclusion criteria have been defined as stated in the Research Plan. The final population will be dependent upon the number of sites within the Network that participate in this study. Both male and female infants will be enrolled. We expect the study population to be representative of the racial background and gender distribution of the Neonatal Research Network. In 2001, 49% male and 51% female patients constituted the ELBW population of the Neonatal Research Network, of which 43% were black, 38% were white, 15% were hispanic, and 3% were other races.

b) Sources of Materials: Sources of research material will consist of perinatal, demographic and neonatal data collected by research personnel as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality Among VLBW Infants (401-1500 g), and through the data collection mechanisms associated with the SUPPORT trial. Additional data will be obtained through evaluation of brain MRI images by a central reader masked to all patient identifiers and patient outcomes. Data forms will be created, completed by the central MRI reader, and submitted to Research Triangle Institute per protocol. Neurodevelopmental outcome data will be obtained from the NICHD Neonatal Research Network Follow-up Study of ELBW Infants, and per SUPPORT specifications.

c) Potential Risks: The risks and discomforts of participation are minimal as the study relies primarily on data collected for ongoing studies already in progress, and uses non-invasive techniques. Cranial US is performed routinely in all NICU's in the NICHD Neonatal Research Network, is considered standard of care, and techniques would not be altered by this study. Brain MRI at 35-42 weeks postmenstrual age is already routine in several Network centers. Sedation will not be used routinely, although may be used particularly in centers that already do use sedation. Temporary minor skin irritation from tape used to apply MRI-compatible monitoring electrodes may occur, but this risk is unlikely. Temporary transport of a patient to a radiology suite for MRI may also represent a possible risk; however, only those patients considered stable for transport will undergo imaging, and a 7- week window of opportunity for MRI is built into

the proposed study. The alternative to obtaining a brain MRI as part of the proposed study is non-enrollment.

2. Adequacy of Protection Against Risks:
a) Recruitment and Informed Consent :
Screening: The individual center will be responsible for devising a screening strategy to identify all potential participants using the study inclusion and exclusion criteria. Screening, identification and informed consent procedures should be completed by 14 days of age as "early cranial US" must be performed by this time.
Informed consent: Each participating center will follow procedures for developing informed consents as set out by their Institutional Review Board (IRB). The parents of all infants enrolled in SUPPORT will be approached to participate in this secondary study, and informed consent must be obtained by the individual center. Informed consent will be obtained by the Principal Investigator or his/her designee.
Eligible infants not enrolled: The reasons for non-enrollment of eligible infants will be documented. Short- and long-term outcomes of eligible infants not enrolled in this study will be documented as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality in Very Low Birth Weight (VLBW) Infants (Generic Data Base (GDB)) and, if enrolled, as part of the ongoing NICHD Neonatal Research Network ELBW Neurodevelopmental Follow-Up Study.
No MRI obtained for enrolled infants: The objective of the proposed study requires acquisition of cranial US and MRI at 35-42 weeks PMA; if the patient is deemed medically unstable during the entire 35-42 week PMA period, an MRI will not be obtained. Other reasons for inability to obtain the MRI will also be documented.
b) Protection against risk: Every effort will be made to protect study patients from potential risks of participation. Stability of study patients for transport to a radiology suite for brain MRI will be assessed by the attending neonatologist at each participating site. Should a patient be judged to be unstable for transport to the radiology suite, a 7-week window of opportunity for MRI (35-42 weeks postmenstrual age) has been provided in the protocol. Any adverse events with regard to obtaining neuroimaging studies among enrolled patients will be documented and submitted to NICHD, the data center, and the local IRB. The NICHD Neonatal Research Network has an independent Data Safety Monitoring Committee (DSMC), which would provide continuous oversight of patient safety and risk factors for the duration of the study. The DSMC will review the study on at least an annual basis.

3. Potential Benefits of the proposed research to the subjects and others: The potential benefits of participation to an individual patient include identification of structural anomalies by MRI that would not have been identifiable by ultrasound. This may allow for early, targeted intervention for the individual patient that otherwise would not have been undertaken. Other potential benefits would be to future extremely preterm patients after results of this prospective study are known (see below).

4. Importance of the knowledge to be gained:
Provide a thorough neuroimaging monitoring arm for SUPPORT: Although cranial US is a standard diagnostic procedure in the NRN, the proposed study would provide a

framework for specifically timed cranial US studies, which would be more appropriately comparable. In addition, subtle but arguably extremely important findings consistent with brain injury would be detectable by MRI.
Counseling, follow-up: Detection of an injury pattern which is consistent with later neurodevelopmental delay will be useful for counseling and targeted, early follow-up. Identifying such a tool would provide a link to later research in early intervention.
Clarify the pathogenesis of injury leading to neurodevelopmental impairment: Further delineation of pathophysiologic correlates of later outcome could possibly be linked with perinatal and neonatal factors, which would 1) focus future research and intervention on clinical events associated with the pathophysiologic hallmark, 2) provide important data leading to further study of the pathogenesis and timing of injury, and 3) assess neuroanatomic localization of subtle injury associated with later neuromotor abnormalities.
Contribution to the literature with respect to diagnostic strategies for the extremely preterm population: Previous neuroimaging practice parameters have concluded that insufficient evidence exists to recommend advanced neuroimaging for premature infants for prediction of neurodevelopmental outcomes. The proposed study would address this significant gap in the collective literature.

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From: Wally Carlo, M.D.
To: Everett, Ruth
Cc: wrich@ucsd.edu; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: pilot oxygenation
Date: Wednesday, December 15, 2004 1:55:59 PM

Ruth: Yes, it is true that there will be many 24-27 week babies who will not qualify but we have had about 1 per week and our units are about the same. We are trying to keep them on CPAP so that may be the difference. To change criteria, we would have to go to the committee and the IRBs after that. We should discuss this on our next conf call. wally

-----Original Message-----
From: Everett, Ruth [mailto:REverett@med.miami.edu]
Sent: Wednesday, December 15, 2004 11:59 AM
To: Wally Carlo, M.D.
Cc: wrich@ucsd.edu
Subject: pilot oxygenation

Hello Dr. Carlo and Wade, I am having some prpoblems with enrolling infants into the pilot oxygenation study due to the strict entry criteria. Currently, I have consented five mothers and most of my infants are fitting the same criteria, either they are on the ventilator with room air or less than 30% within the first week of life most likely due to surfactant administration. Also, the infants who require more than 30% oxygenation are greater than 7 days of age when the PDA is open or suspected sepsis. So, my question to you is; are there anyway I can enroll these babies post 7 days or put the monitor on them while they are recieving room air? Currently, I have two of the five babies who are still within my seven day window. One of them is on CPAP with room air and probably will be off respiratory support soon, and the other one is minimal mechanical support including room air. Please help! any suggestions because the consent process is not a problem and we do have babies on mechanical ventilation and CPAP but they are not fitting this criteria. Also, both of these babies were born at the beginning of this week and I thought the oxgen requirements would have increased. So, I need a response as soon as posible before they are out of my window which will be Sunday and Monday.

From: Neil Finer
To: "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"
Subject: FW: Oximeter Study Proposal
Date: Monday, December 13, 2004 5:52:13 PM
Attachments: ucsd1.doc

Hello Everyone
Here is the revised algorithm. This brings us back to reality at 84% and 96% and would allow us to move ahead without an IRB resubmission.
Please let me know if you approve within the next 48 hrs.
Regards
Neil

-----Original Message-----
From: Walt Weber [mailto:WWeber@masimo.com]
Sent: Monday, December 13, 2004 2:46 PM
To: 'nfiner@ucsd.edu'; 'maynard.rasmussen@sharp.com'; 'wrich@ucsd.edu'
Cc: Ammar Al-Ali; Mike Petterson; Maribeth Sayre
Subject: RE: Oximeter Study Proposal

To all concerned,

Based on UCSD's input, I have revised the oximeter study specification to make all oximeters return to normal at 84 %. As can be seen in the first figure, of the attached document, we might expect a marginal improvement over the first set of study oximeters. I have asked Wade to set up a conference call between UCSD and Masimo to discuss the document. -Walter

<<ucsd1.doc>>

> -----Original Message-----
> From: Walt Weber
> Sent: Wednesday, December 08, 2004 1:36 PM
> To: 'nfiner@ucsd.edu'; 'maynard.rasmussen@sharp.com'; 'wrich@ucsd.edu'
> Cc: Ammar Al-Ali; Mike Petterson
> Subject: Oximeter Study Proposal
>
> Please review and provide Masimo with your feedback. Thank you! -Walter
>
> << File: ucsd.doc >>
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>
> **********
>
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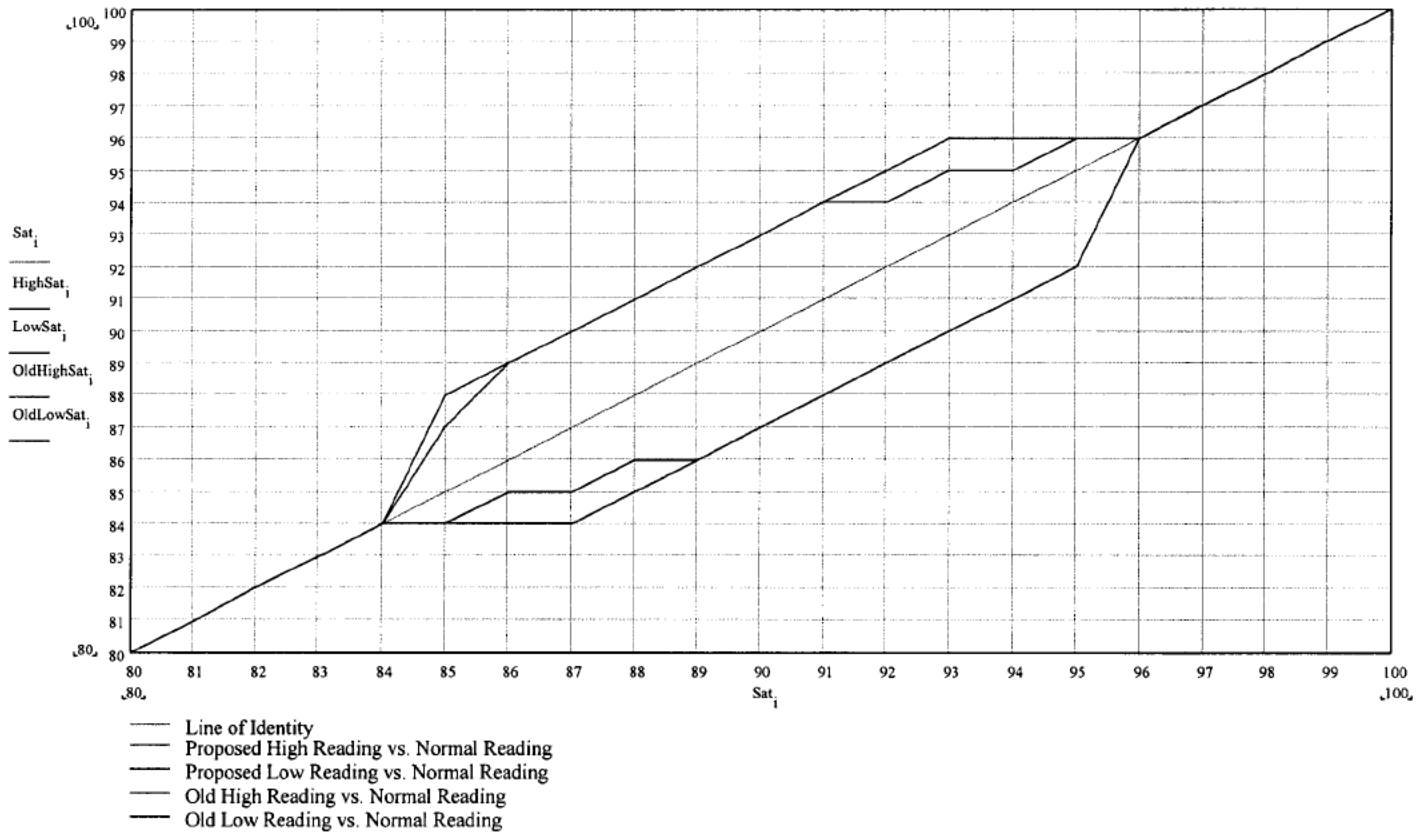
> regular mail to Masimo, 40 Parker, Irvine, California, U.S.A. 92618.
> Thank you.
>
>
>
>

Converting Actual Readings to Low and High Readings

Actual Reading	To Low Reading	To High Reading
100	100	100
99	99	99
98	98	98
97	97	97
96	96	96
95	92	96
94	91	96
93	90	96
92	89	95
91	88	94
90	87	93
89	86	92
88	85	91
87	84	90
86	84	89
85	84	88
84	84	84
83	83	83
82	82	82
81	81	81
80	80	80
etc	etc	etc



The Low, Actual & High Reading oximeters synchronize for values greater than or equal to 96 % and less than or equal to 84 %.

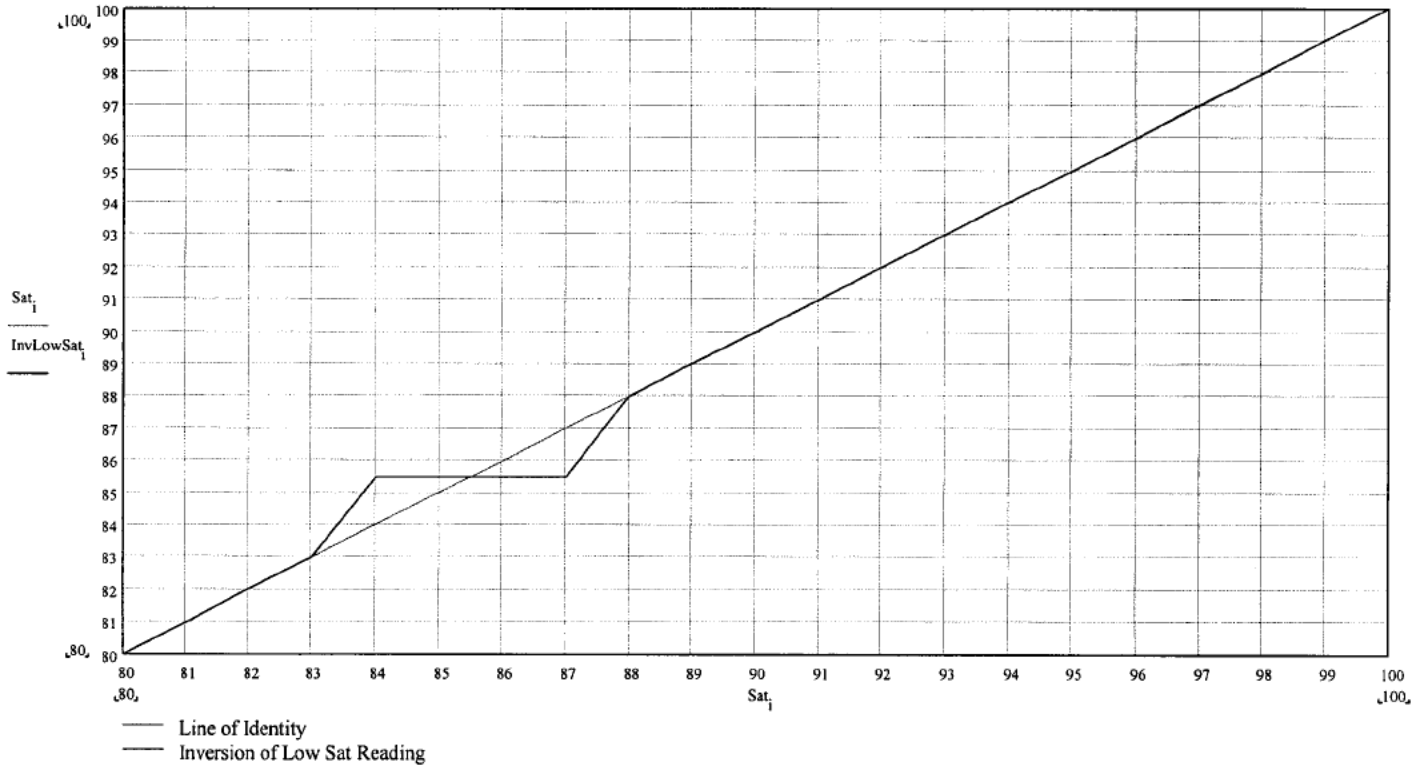
In the Actual range of 87 % to 95 %, the Low Reading Oximeter displays a value 3 points below actual.

In the Actual range of 85 % to 93 %, the High Reading Oximeter displays a value 3 points above actual.

Converting Low Readings to Normal Readings

Low Reading	To Normal Reading
100	100
99	99
98	98
97	97
96	96
95	95.75
94	95.50
93	95.25
92	95
91	94
90	93
89	92
88	91
87	90
86	89
85	88
84	85.5
83	83
82	82
81	81
80	80
etc	etc

Applying the above inversion yields the following performance:

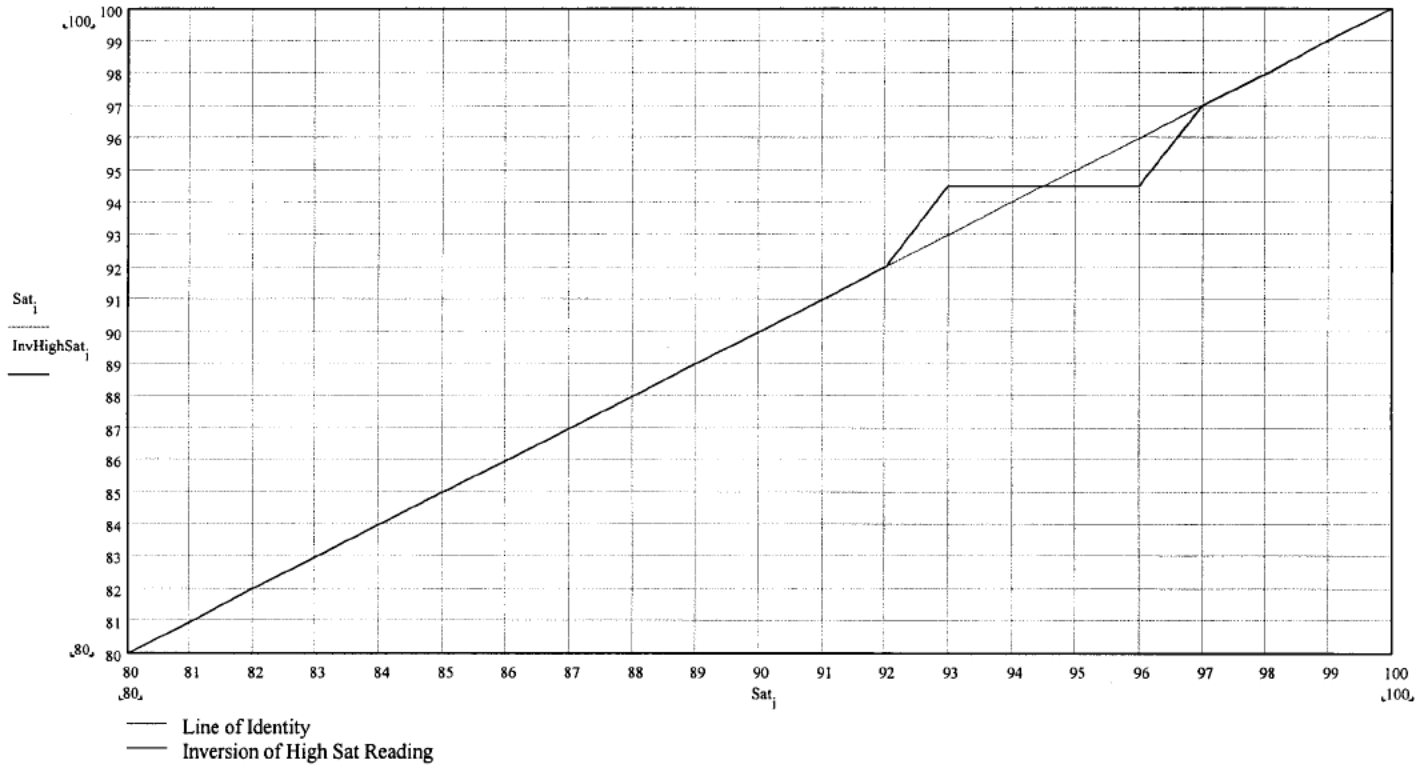


The inversion has no error above and below an actual reading of 88 % and 83 %, respectively. In between these limits, the inversion error does not exceed 1.5 %. Subjects are typically kept in the region of 91 % (88 % + 3 %) to 95 % (92 % + 3 %).

Converting High Readings to Actual Readings

High Reading	To Actual Reading
100	100
99	99
98	98
97	97
96	94.5
95	92
94	91
93	90
92	89
91	88
90	87
89	86
88	85
87	84.75
86	84.50
85	84.25
84	84
83	83
82	82
81	81
80	80
etc	etc

Applying the above inversion yields the following performance:



The inversion has no error above and below an actual reading of 97 % and 92 %, respectively. In between these limits, the inversion error does not exceed 1.5 %. Subjects are typically kept in the region of 85 % (88 % - 3 %) to 89 % (92 % - 3 %).

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: FW: SUPPORT call (2 of 2) Thur. Dec 9, 10-11am ET (7-8amPT)
Date: Thursday, December 09, 2004 10:56:23 AM
Attachments: SUPPORT TRIAL auditing compliance visits.doc

Suggestions for the auditing are also included in the attachment. Wally

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From: Wally Carlo, M.D.
Sent: Thursday, December 09, 2004 8:14 AM
To: 'Higgins, Rosemary (NIH/NICHD)'; 'Petrie, Carolyn'; Ed Donovan (E-mail); Duara, Shahnaz; Michele Walsh; nfiner@ucsd.edu; Poole, W. Kenneth; reverett@med.miami.edu; wrich@ucsd.edu
Cc: Marsha Sumner; diane.timmer@cchmc.org; aellison@med.miami.edu; axt25@po.cwru.edu; fmartinez@ucsd.edu; Hastings, Betty J.; Das, Abhik
Subject: RE: SUPPORT call (2 of 2) Thur. Dec 9, 10-11am ET (7-8amPT)

We are getting (b) (6) within the next hour so I may not be able to be on the call. I have added a suggestion to the working template.
Suggestion to improve the percent of time babies are kept with saturations 88-92% are:
1) Tighter alarm limits (e.g. 85-95% or 86-94% or even 87-93%). It would be easy to use alarms at 85 and 95 because many monitors and physicians use these limits (even though they have a different meaning on the Maximos).
2) Immediate feedback to clinical MDs, RNs, RTs, and residents upon completion of each pilot baby (ideally even before they enroll the next one).
3) Cumulative feedback with each addition of a pilot baby.
4) Comparison feedback by showing data from all centers.
5) Frequent (once a week) emails to all sites updating on enrollment and compliance with saturations in the pilot study.
Wally

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, December 08, 2004 8:43 AM
To: 'Petrie, Carolyn'; Wally Carlo, M.D.; Ed Donovan (E-mail); Duara, Shahnaz; Michele Walsh; nfiner@ucsd.edu; Poole, W. Kenneth; reverett@med.miami.edu; wrich@ucsd.edu
Cc: Marsha Sumner; diane.timmer@cchmc.org; aellison@med.miami.edu; axt25@po.cwru.edu; fmartinez@ucsd.edu; Hastings, Betty J.; Das, Abhik
Subject: RE: SUPPORT call (2 of 2) Thur. Dec 9, 10-11am ET (7-8amPT)

Here is a working template for the monitoring.
Rose

-----Original Message-----
From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Wednesday, December 08, 2004 9:42 AM
To: Petrie, Carolyn; wcarlo@peds.uab.edu; Ed Donovan (E-mail); Duara, Shahnaz; Michele Walsh; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; reverett@med.miami.edu; wrich@ucsd.edu
Cc: msumner@peds.uab.edu; diane.timmer@cchmc.org; aellison@med.miami.edu; axt25@po.cwru.edu; fmartinez@ucsd.edu; Hastings, Betty J.; Das, Abhik
Subject: RE: SUPPORT call (2 of 2) Thur. Dec 9, 10-11am ET (7-8amPT)

Reminder for tomorrow's call:

The second SUPPORT conference call to discuss the site monitoring visits is scheduled for

Thursday, December 9th
10:00-11:00am ET (7-8am PT)

If you are unable to attend this call, please circulate your comments.

To join the call:
Dial Tollfree: **866-675**(b) (6)
Passcode: (b) (6) (# when prompted)

Leader: Rose Higgins

Thank you,
Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

SUPPORT TRIAL auditing compliance visits

RTI along with medical personnel will visit the SUPPORT sites to determine adherence and protocol compliance.

Specific items to be assessed:

1. Delivery room practice following randomization
2. Adherence to protocol with respect to details including time sensitive issues, ie criteria followed for 14 days, intubation for appropriate criteria, weaning appropriately towards extubation criteria, extubation for appropriate criteria, obtaining blood gases as requested, following criteria for reintubation, use of nasal SIMV only following extubation, and so forth.
3. Appropriate initial timing of surfactant dosing - < 1 hour for Control infants.
4. Accuracy of data collection
5. Adherence to compliance with eye examinations
6. Appropriate pulse oximetry alarm limits and utilization of study oximeters
7. Post natal steroid use
8. Head ultrasound compliance between day 4-21
9. Percentage of time oxygen saturations are in the 88-92% range and % of time they are within the alarm limits.

Formatted: Bullets and Numbering

From: Wally Carlo, M.D.
To: Neil Finer; Abbot Laptook
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Jon.E.Tyson@uth.tmc.edu
Subject: RE: Support
Date: Tuesday, November 09, 2004 7:15:40 PM

Neil: I agree with you. wally

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, November 09, 2004 10:21 AM
To: Wally Carlo, M.D.; Abbot Laptook
Cc: HigginsR@mail.nih.gov; Jon.E.Tyson@uth.tmc.edu
Subject: Re: Support

Thanks Wally
I would only add that the noise of different site oximeter and oxygen management cannot be utilized in any prospective analysis, and yet these differences, as noted by Wally #3, are substantial. We will restrict these options and allow analysis by oxygen management for these outcomes. I fail to see how excluding one arm makes this trial stronger. I believe that the opposite is true.
Regards
Neil

----- Original Message -----
From: Wally Carlo, M.D.
To: Abbot Laptook ; nfiner@ucsd.edu
Cc: HigginsR@mail.nih.gov ; Jon.E.Tyson@uth.tmc.edu
Sent: Tuesday, November 09, 2004 6:42 AM
Subject: RE: Support

Abbot:

Important reasons for the factorial design are (as I see it):

1) O2 sats have to be controlled in a ventilation trial anyway (as we have done in all previous trials),
2) As two different ventilation strategies may result in different FiO2/sats so unless these are controlled, the groups may receive different oxygenation support which may reduce the effect size of the different ventilator strategies on the primary outcome but the data on their oxygenation intervention would be unknown,
3) In general, many clinicians use ventilatory and oxygenation strategies (among other strategies) to minimize lung injury/BPD while maintaining infants alive. Thus, a factorial design is ideal to give these two treatments/interventions together.
4) If each intervention is tested separately, it may be necessary still to test them together to detect the safety and efficacy of their combined use as they would be used clinically,
5) We can take advantage of the opportunity of doing two trials at the same time while making each trial better as the other parts of the vent/oxygenation strategies will be controlled and known.

Disadvantages include possible positive or negative interactions but it would be preferable for a trial to be able to sort out any interaction than only realizing after the conclusion of the trial that the interaction was (or was not) important.

Jon may come up with other pros and cons.

Hope this helps.

From: Abbot Laptook [mailto:ALaptook@WIHRI.org]
Sent: Tuesday, November 09, 2004 8:06 AM
To: Wally Carlo, M.D.; nfiner@ucsd.edu
Cc: HigginsR@mail.nih.gov
Subject: Support

Wally, Neil,
Maybe you can help me with the following issue regarding rationale for the design of the support trial. I was at a meeting talking with Scott Denne and he was concerned over the factorial design. I tried to justify it by the argument that by randomizing the pulse ox arm, there will be less background noise for interpreting the ventilation arm and at the same time with little effort we will get valuable information regarding O2 sats and ROP. His concern was that the outcomes of BPD and ROP are not independent, and given that the study will not be powered to detect interactions between these two outcomes, this will be a critical limitation. How would you counter this argument? Let me know, Tx, Abbot

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Outgoing mail is certified Virus Free.
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Version: 6.0.786 / Virus Database: 532 - Release Date: 10/29/2004

From: Wade Rich
To: "Neil Finer"; "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Ken Poole"; "Michele"; "Shahnaz Duara"
Cc: "Mike Petterson"; "Walt Weber"
Subject: RE: SpO2 tables
Date: Wednesday, December 08, 2004 6:18:28 PM
Attachments: ucsd.doc

Dear Support Committee:

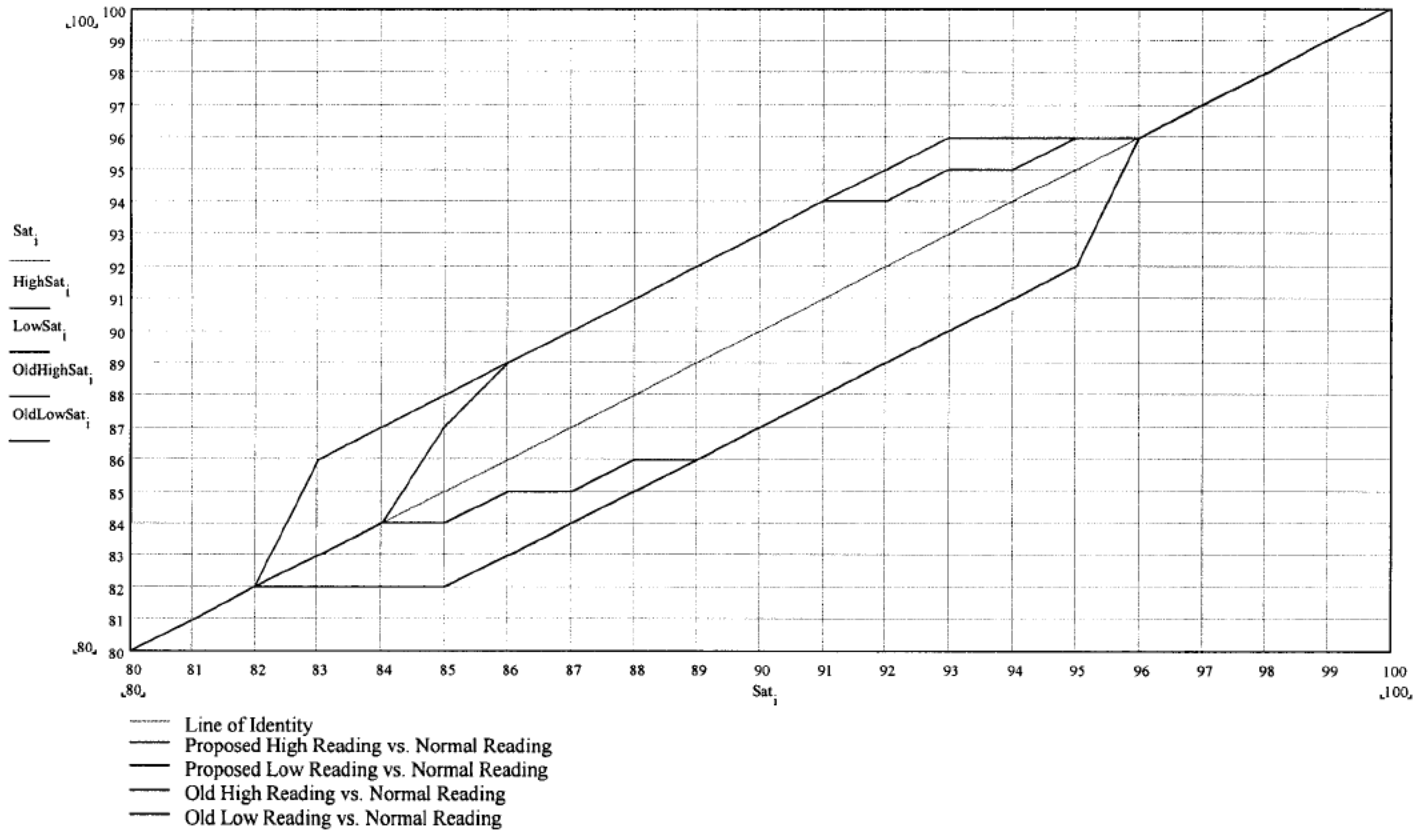
Attached is the revised skew that Masimo has sent back to us. Please review and see what you think. We would propose leaving the alarms as previously established. (84 and 96) This will mean the monitors alarm at slightly different values for the high and low reading oximeters. For example, the low reading oximeter will low alarm at a true value of 87 while the high reading will alarm at a true value of 82.5

Read and enjoy. Happy Holidays!

Wade and Neil

Converting Actual Readings to Low and High Readings

Actual Reading	To Low Reading	To High Reading
100	100	100
99	99	99
98	98	98
97	97	97
96	96	96
95	92	96
94	91	96
93	90	96
92	89	95
91	88	94
90	87	93
89	86	92
88	85	91
87	84	90
86	83	89
85	82	88
84	82	87
83	82	86
82	82	82
81	81	81
80	80	80
etc	etc	etc



The Low, Actual & High Reading oximeters synchronize for values greater than or equal to 96 % and less than or equal to 82 %.

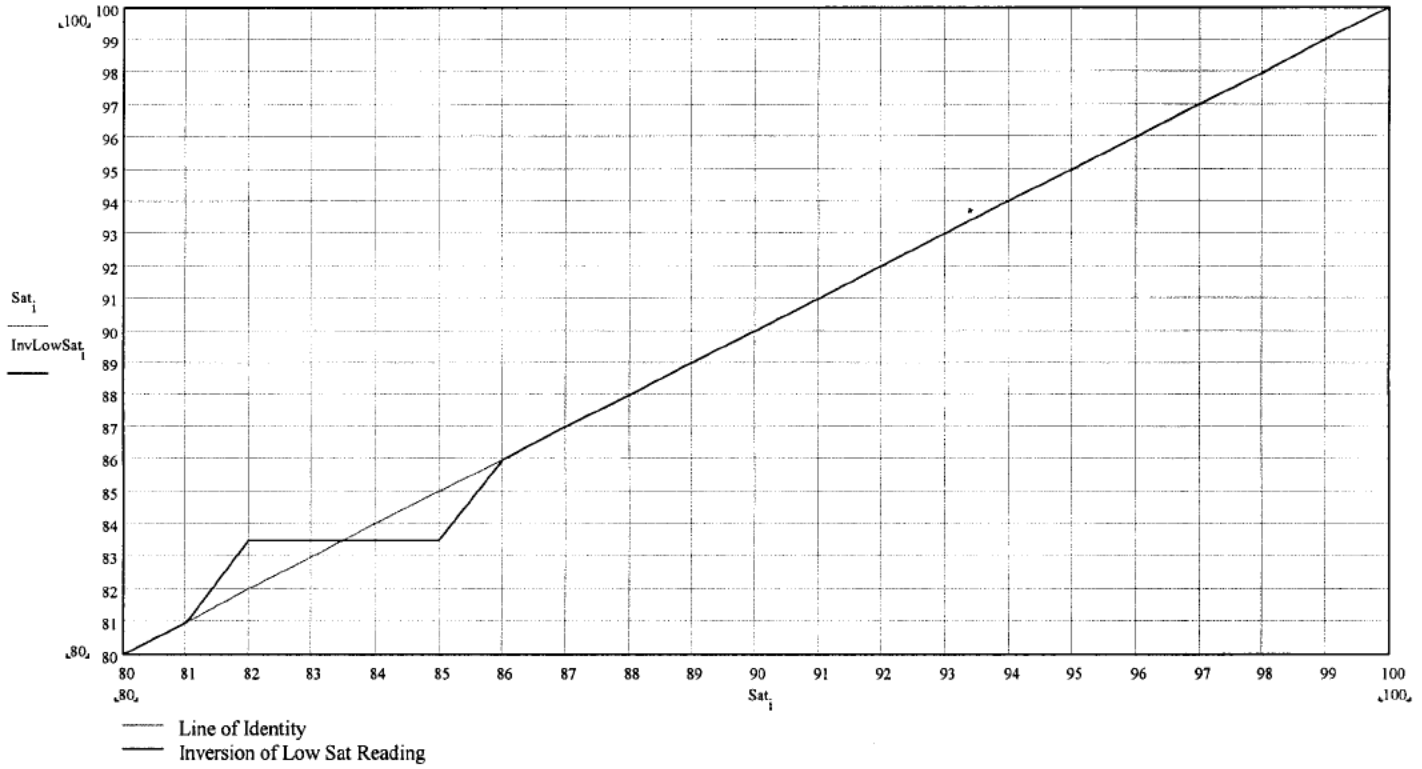
In the Actual range of 85 % to 95 %, the Low Reading Oximeter displays a value 3 points below actual.

In the Actual range of 83 % to 93 %, the High Reading Oximeter displays a value 3 points above actual

Converting Low Readings to Normal Readings

Low Reading	To Normal Reading
100	100
99	99
98	98
97	97
96	96
95	95.75
94	95.50
93	95.25
92	95
91	94
90	93
89	92
88	91
87	90
86	89
85	88
84	87
83	86
82	83.5
81	81
80	80
etc	etc

Applying the above inversion yields the following performance:

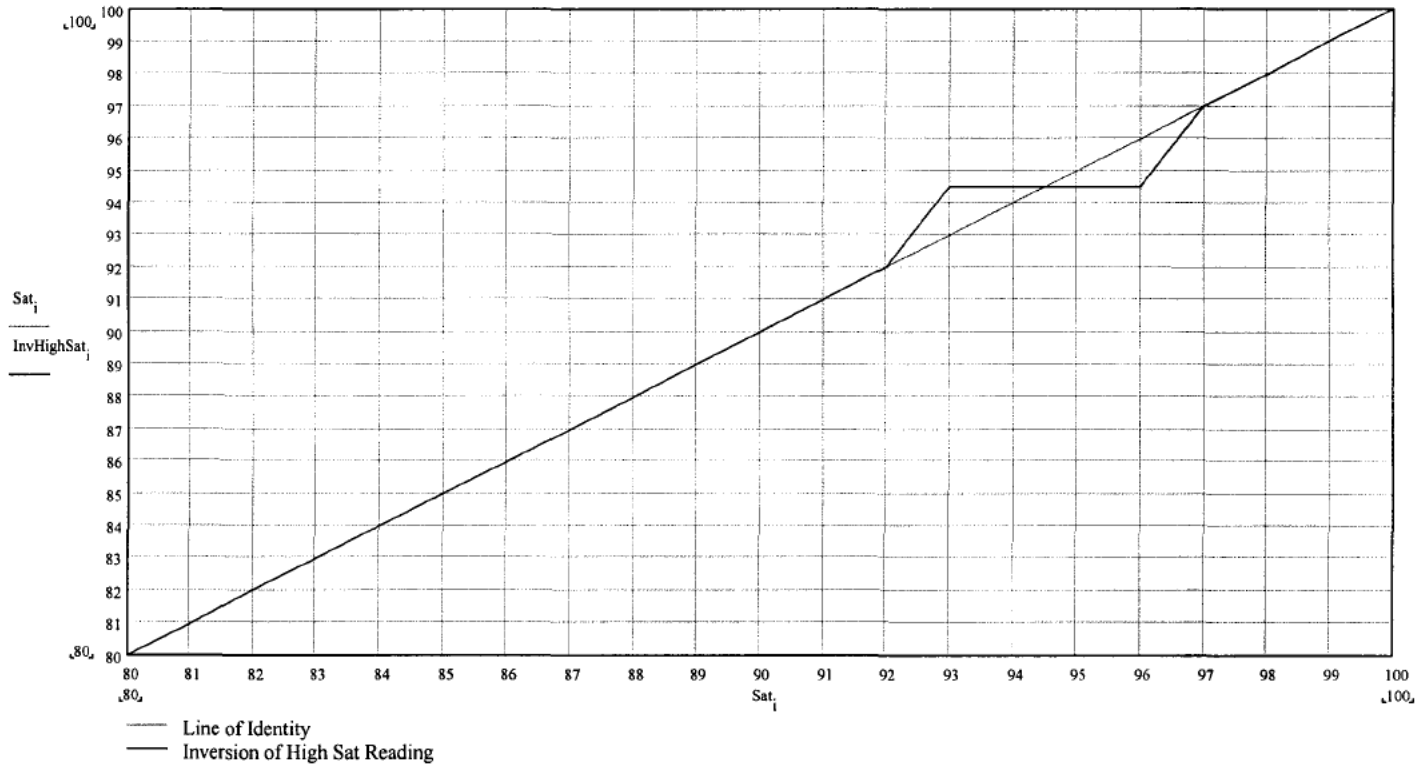


The inversion has no error above and below an actual reading of 86 % and 81 %, respectively. In between these limits, the inversion error does not exceed 1.5 %. Subjects are typically kept in the region of 91 % (88 % + 3 %) to 95 % (92 % + 3 %).

Converting High Readings to Actual Readings

High Reading	To Actual Reading
100	100
99	99
98	98
97	97
96	94.5
95	92
94	91
93	90
92	89
91	88
90	87
89	86
88	85
87	84.
86	83
85	82.75
84	82.50
83	82.25
82	82
81	81
80	80
etc	etc

Applying the above inversion yields the following performance:



The inversion has no error above and below an actual reading of 97 % and 92 %, respectively. In between these limits, the inversion error does not exceed 1.5 %. Subjects are typically kept in the region of 85 % (88 % - 3 %) to 89 % (92 % - 3 %).

From: Berberich, Mary Anne (NIH/NHLBI)
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: DSMC Report 12-6-04.doc
Date: Tuesday, December 07, 2004 3:24:18 PM

Hi Rose,

Did the DSMB decide how often they will meet ? Will there be quarterly accrual reports? analysis of adverse events? When you have a few minutes to discuss the study timetable etc. please give me a call at 435-0219.

Thanks,
Mary Anne

-----Original Message-----
From: Kiley, James (NIH/NHLBI)
Sent: Tuesday, December 07, 2004 2:59 PM
To: Berberich, Mary Anne (NIH/NHLBI)
Cc: Gail, Dorothy (NIH/NHLBI)
Subject: RE: DSMC Report 12-6-04.doc

Thanks for this brief summary. It will be important for you to send me regular updates on the progress of this study, so i can keep bldg 31 in the loop. i don't want to hear about what is going on for the1st time when there is a problem. please let me know what the current timetable is for this study and what would be reasonable time points for updates. thanks, jim

-----Original Message-----
From: Berberich, Mary Anne (NIH/NHLBI)
Sent: Tuesday, December 07, 2004 2:38 PM
To: Kiley, James (NIH/NHLBI)
Subject: DSMC Report 12-6-04.doc

FYI

The first meeting of the DCC for the NICHD/NHLBI CPAP (SUPPORT) study took place via teleconference yesterday. Rose and I were permitted to listen in on the general discussion, before the committee went into executive session. As you may recall, NHLBI has 3 ad hoc representatives on the standing DCC for the NICHD Network: John Hunt, Marilee Allen and Merran Thompson, who were all present. Merran Thompson is most experienced in the study approach since she has participated in a similar study in the UK. Her comments were very helpful to the P.I. during a review of the protocol performed to ensure proper monitoring.

RTI INTERNATIONAL | **Memorandum**

December 7, 2004

TO: Network Coordinators
Network PIs

FROM: The Data Coordinating Center

SUBJECT: The Data Safety and Monitoring Committee (DSMC) meeting on the SUPPORT Protocol

The SUPPORT DSMC met on December 6 at 4:00PM to review the study protocol. Dr. Finer conducted a careful and detailed discussion of the research plan and fielded questions from the DSMC members. In closed session, the Committee agreed the study should go forward and congratulated the Network on undertaking this important and complicated study.

cc: Rosemary Higgins, MD
Marian Willinger, PhD
Mary Ann Berberich, MD

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: dstevenson@stanford.edu
Subject: comments from SUPPORT secondary
Date: Tuesday, December 07, 2004 1:24:01 PM

Rose,

Just looking again at some of the neuroimaging comments -

- Please reiterate to the group that the "scoring" system - both for the HUS and for MRI - is NOT WRITTEN IN STONE. Truly, this aspect of the protocol will be thoroughly evaluated as soon as we know which direction things are going - as you know, the question of whether HUS would be centrally read was very much up in the air, although i feel it is crucial as is the MRI central reading. If we use a scoring format for the HUS similar to the PiNO HUS scoring form, we will capture a huge amount of important information. As soon as we have an answer about the protocol, I will ask Dorothy Bulas and Tom Slovis to weigh in about their perception re: what should be CHANGED on that form. I have also asked Abbot Laptook to share the aEEG MRI scoring form, and give his input (along with Seetha) about what items are "must haves" for any MRI scoring form.

- Another issue that Abbot brought up was that Brown apparently does not routinely perform even HUS at near term unless there were "problems" on early HUS. That comes as a bit of a shock, especially since the Neuroimaing Practice Parameter recommends that rescreening should "optimally occur at 36-40 weeks PMA". I assumed that everyone in the Network would have implemented this recommendation. This may lead to even further concerns on the part of some of the PI's re: cost.

Thanks Rose!

Susan
--
Susan R. Hintz, M.D.
Assistant Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: dstevenson@stanford.edu
Subject: Re: MRI secondary comments
Date: Monday, December 06, 2004 11:05:25 PM

Hi Rose,

Thanks for the information. In reviewing this and other brief comments, it appears that the readers feel that the study is "all or nothing" with respect to the MRI. As we both know, the extent of the MRI portion participation depends greatly on the $$ aspect, but very useful information could STILL be obtained regarding predictive modeling of outcomes with early and late cranial US. I hope it is clear in the proposal that will still be able to participate in JUST the cranial US portion if MRI funding is not possible for all centers.

Also - Rose do you want me to fax the final abstract to you? Both are submitted - although I notice they extended the deadline.

Thanks,

Susan

> Susan and David:
> As you know, the voting continues for the MRI secondary to SUPPORT. I will let you know the results as soon as we have a quorum of votes. If substantive comments come in with the votes, I will forward them to you as I receive them - here is one set of comments:
>
> We are strongly supportive of the science to be learned, and we believe we could participate in the secondary study. However, it is not routine in our institution to obtain a near term MRI on preterm infants, so we would need financial support for this (at least as of today's understanding).
> We also suggest:
> 1. In the grading of severity of IVH by ultrasound, please consider the scoring proposed by Volpe. Reference: Neurology of the newborn, 4th edition, Joseph J. Volpe, MD pp 451 table 11-13. This is Volpe's classification, as he states in his chapter. He does not provide any other reference. As IVH is not always symmetrical, I am hoping that central scoring process will look at left and right and not score by worst side.
> Nirupama
> 2. That consent for participation in the MRI (non-standard and possibly needing sedation) be obtained later in the hospital course. There is just too much in the original consent now (oxygen and CPAP and follow up) to put this in, even as an opt out.... unless maybe they have a choice of: yes, no, maybe-ask me later.
> Rosemary D. Higgins, M.D.
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine NICHD, NIH
> 6100 Executive Blvd., Room 4B03B
> MSC 7510
> Bethesda, MD 20892
> (for Fed X use Rockville, MD 20852)

301-435-7909
301-496-3790 (FAX)

--
Susan R. Hintz, M.D.
Assistant Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite #315
Palo Alto, CA 94304

phone: 650-723-5711
fax: 650-725-8351

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SpO2 tables
Date: Friday, December 03, 2004 10:22:56 AM

Rose: THANKS. Can you send me the table? Wally

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 03, 2004 9:21 AM
To: Wally Carlo, M.D.
Subject: FW: SpO2 tables

-----Original Message-----
From: Neil Finer [mailto:nfiner@pedsmail.ucsd.edu]
Sent: Friday, December 03, 2004 9:52 AM
To: Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; Higgins, Rosemary (NIH/NICHD); Ken Poole; Michele; Neil Finer; Shahnaz Duara; Wade Rich
Subject: FW: SpO2 tables

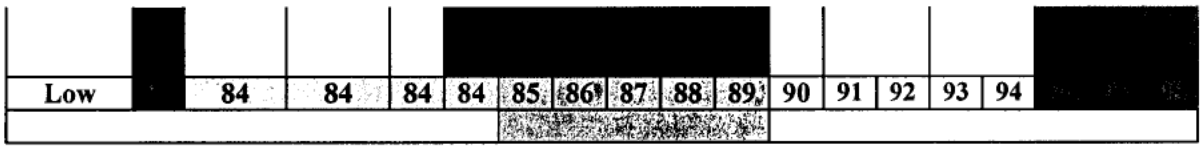
For todays call
Neil

From: Neil Finer
Sent: Thursday, December 02, 2004 8:38 AM
To: 'Mike Petterson'
Cc: 'ccole@bidmc.harvard.edu'; 'wrich@UCSD.Edu'; Maynard Rasmussen (maynard.rasmussen@sharp.com)
Subject: RE: SpO2 tables

Good Morning Mike
As you may have heard, we completed our pilot looking at the separation of the trial oximeters. In a nutshell, they work as designed, and many thanks to you and Amar and your team and for Masimo for supporting this project. We have been impressed with your professionalism, and commitment to these studies.
The problem is that we do not think that we are getting adequate separation, and thus we will probably not see a difference in the oxygen exposure of the infants. I am attaching an Abstract from Maynard who did this pilot and the results show that we are not in the narrow range (88-92%) more than 30% of the time, and it is in that range that the SpO2 differ maximally.
I have given this significant thought and discussed this with Cindy Cole. We have designed another iteration that would keep the 2 oximeters at least 3% away from the actual for a much larger range, and yet still allow a return to normal values. This return would occur over a shorter SpO2 range, but with the 16 second averaging, may not be all that recognizable,
Could you look at these, and I will try to call you later. (Ignore the colors)

The hi reading probe retains a 3% offset from 86% to 92% (real values) and the low reading is 3% offset for values from 87% to 93%, giving much better separation for a larger range. The original scheme had a 3% separation only at 90% and then decreased back to none by the limits.

High		**85**	**86**	**87**	**88**	**89**	**90**									
Standard		**84**		**85**		**86**	**87**	**88**	**89**	**90**	**91**	**92**	**93**	**94**	**95**	



Draft Preview of Abstract #751472
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First Author: Maynard R Rasmussen

File Number: 751472

Presenting Author: Maynard R Rasmussen

Subspecialty: Neonatology - General

Theme: Clinical Trials in Perinatal and Neonatal Medicine

2005 Pediatric Academic Societies' Meeting

Consider for Eastern SPR: No, Do not consider this abstract for the Eastern SPR.

Contact Person: Neil Finer, MD

Department/Institution/Address: Neonatology, University of California San Diego, San Diego, Ca, United States

Phone: Fax: E-mail: nfiner@ucsd.edu

Presenter E-mail: maynard.rasmussen@sharp.com

Disclosure:
Maynard Rasmussen has nothing to disclose.
Wade Rich needs to complete disclosure information.
Gregory Rasmussen has nothing to disclose.
Neil Finer has nothing to disclose.

Awards Applied for:
Consider for PAS Travel Grant Award: No

APA, Special Interest Groups, Committees or Regions:

Keywords: oxygen; oximeter;
Is First Author a Trainee? No, Not a Trainee
Research type: Clinical
Presentation conflict on: No conflict

Title: Prospective Evaluation of Altered Pulse Oximeters Designed to Produce Different Oxygen Exposures for ELBW Infants: Preparation for the SUPPORT Trial.

Maynard R Rasmussen, MD [1,2], Wade Rich [2], Gregory S Rasmussen, BS [2] and Neil Finer, MD [2]. [1] Neonatology, Sharp Mary Birch Hospital for Women, San Diego, California, United States, 92123; [2] Neonatology, University of California, San Diego, San Diego, California, United States and [3] NICHD Neonatal Research Network.

Background: No prospective studies have evaluated the effect of higher vs. lower SpO2 ranges in ELBW infants from birth. The SUPPORT trial will randomize ELBW infants to different SpO2 ranges within 2 hours of birth, using altered Masimo oximeters (Masimo Corp, Irvine, Ca), programmed to display falsely high or low SpO2 values in the range of 85-95%, with a maximum difference of 6% (90% displays 87% or 93%). The displayed range of 88-92% will correspond to actual values of either 85%-89% or 91%-95%.

Objective: To test the performance of altered oximeters on ELBW infants prior to the SUPPORT trial to ensure that an adequate separation of SpO2 is achieved.

Design/Methods: Oximeter performance was evaluated on 20 hemodynamically stable ELBW infants receiving positive pressure support, using standard Masimo oximeters (Ox). Sensors from a standard and a masked (high or low reading) Ox were attached one to each lower extremity. Ox alarms were 84% and 96% with a target SpO2 range of 88% to 92%. Extremities were switched every 6 hours and altered oximeters switched after 12 hours. The averaging mode was 16 seconds, data sampling every 10 seconds and data was collected for 24 hours. Data points were matched to the nearest second.

Results: 1. Contemporaneous Ox data demonstrated of 4.5% difference in mean SpO2s of altered Oxs at a standard SpO2 of 90%. The difference between the altered Oxs decreased to <2% for standard SpO2 values of less than 84% and greater than 96%. **2.** Motivated caretakers were successful at maintaining a target SpO2 of 88-92% for only 29% of the time. Patients approximately spent 10% of time < 84%, 10% between 84% and 87%, 40% between 93% and 96% and 9% of time >96%. **3.** Using the altered oximeters would have resulted in minimal separation of the displayed versus actual SpO2, and minimal differences in oxygen exposure.

Conclusions: Altered Oxs performed as designed, but demonstrated less clinical separation than anticipated, probably due to saturation averaging and decreasing differences in SpO2s as 84% and 96% are approached. To achieve a significant difference in oxygen therapy between groups, we believe that a maximal separation of 6% over a wider range of SpO2s is desirable.

Thanks
Neil Finer

From: Neil Finer
To: Avroy A. Fanaroff, M.D.; Betty Hastings; Ed Donovan; Higgins, Rosemary (NIH/NICHD) [E]; Ken Poole; Michele; Neil Finer; Shahnaz Duara; Wade Rich
Subject: FW: SpO2 tables
Date: Friday, December 03, 2004 9:51:53 AM
Attachments: New Oximeter Skew Nov 30 04.ppt

For todays call
Neil

From: Neil Finer
Sent: Thursday, December 02, 2004 8:38 AM
To: 'Mike Petterson'
Cc: 'ccole@bidmc.harvard.edu'; 'wrich@UCSD.Edu'; Maynard Rasmussen (maynard.rasmussen@sharp.com)
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First Author: Maynard R Rasmussen

Presenting Author: Maynard R

File Number: 751472

Rasmussen

Subspecialty: Neonatology - General

Theme: Clinical Trials in Perinatal and Neonatal Medicine

2005 Pediatric Academic Societies' Meeting

Consider for Eastern SPR: No, Do not consider this abstract for the Eastern SPR.

Contact Person: Neil Finer, MD

Department/Institution/Address: Neonatology, University of California San Diego, San Diego, Ca, United States

Phone: Fax: E-mail: nfiner@ucsd.edu

Presenter E-mail: maynard.rasmussen@sharp.com

Disclosure:
Maynard Rasmussen has nothing to disclose.
Wade Rich needs to complete disclosure information.
Gregory Rasmussen has nothing to disclose.
Neil Finer has nothing to disclose.

Awards Applied for:
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APA, Special Interest Groups, Committees or Regions:

Keywords: oxygen; oximeter;
Is First Author a Trainee? No, Not a Trainee
Research type: Clinical
Presentation conflict on: No conflict

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Maynard R Rasmussen, MD [1,2], Wade Rich [2], Gregory S Rasmussen, BS [2] and Neil Finer, MD [2]. [1] Neonatology, Sharp Mary Birch Hospital for Women, San Diego, California, United States, 92123; [2] Neonatology, University of California, San Diego, San Diego, California, United States and [3] NICHD Neonatal Research Network.

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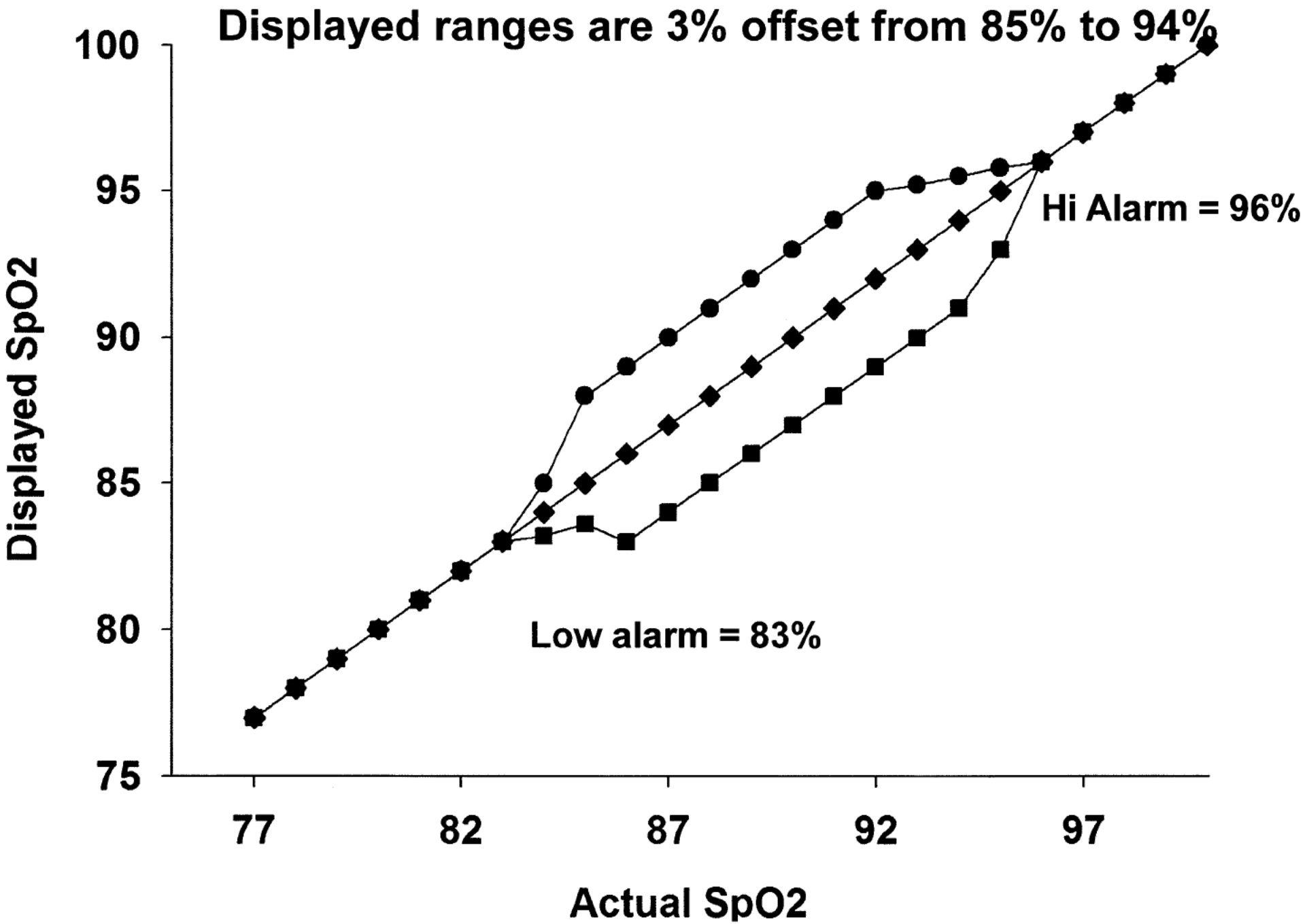
Thanks
Neil Finer



From: Debra Brandon
To: nfiner@ucsd.edu
Cc: "Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; "Ronald GOldberg "; Higgins, Rosemary (NIH/NICHD) [E]; "Michele"; "Neil Finer"; "Ken Poole"; "Shahnaz Duara"; "Wade Rich"; Kathy J Auten
Subject: RE: Support Trial
Date: Thursday, December 02, 2004 12:58:09 PM
Attachments: Cycled light - Duke.doc

Neil,

Thanks for your prompt response. I think you misunderstood the target population for the cycled light study. We are enrolling infants < or = 28 weeks. Therefore, the 23 and 24 week infants are in the study more than 9 weeks. ROP is included as a safety outcome and while we are hypothesizing no difference between the intervention groups, I understand your position. I will work with Ron and Kathy Auten to develop and enrollment equity approach to ensure both studies have fair access to the population of interest.

Thanks and good luck,

Debbie Brandon RN, PhD, CCNS
Neonatal Program Director
Assistant Professor
919-681-3813 voicemail
919-970-(b) (6)pager

"Neil Finer"
<nfiner@ucsd.edu>
12/02/2004 12:44 PM
Please respond to <nfiner@ucsd.edu>

To: "'Debra Brandon'" <brand005@mc.duke.edu>
cc: "'Ronald GOldberg '" <goldb008@mc.duke.edu>, "'Avroy A. Fanaroff, M.D.'" <aaf2@po.cwru.edu>, "'Betty Hastings'" <bkh@rti.org>, "'Ed Donovan'" <Edward.Donovan@chmcc.org>, <higginsr@mail.nih.gov>, "'Ken Poole'" <poo@rti.org>, "'Michele'" <mcw3@po.cwru.edu>, "'Neil Finer'" <nfiner@ucsd.edu>, "'Shahnaz Duara'" <sduara@miami.edu>, "'Wade Rich'" <wrich@ucsd.edu>

Subject
RE: Support Trial

Hello Debra
I have reviewed your trial. The main problems are that ROP is an outcome of interest in your trial and the SUPPORT trial and in addition neurodevelopmental outcome is also an outcome for SUPPORT. Since your study is not done at all other centers this would create an additional cofactor for infants enrolled at DUKE and thus the outcomes of ROP and neurodevelopment may be affected by both. In addition the enrollments in both studies will not be balanced to ensure that equal numbers of SUPPORT infants are enrolled equally in either arm of your trial. SUPPORT is complicated by having 4 discrete arms making this even more difficult. The study entry criteria will be similar to SUPPORT although SUPPORT will not enroll infants of 28 weeks or greater.
I did not understand the durations of cycling as most infants of 27-28 weeks
are in the nurseries for usually 6-9 weeks and yet you indicate much longer for cycling and non-cycling. Is your length of stay that long for infants of
27 to 28 weeks?
Overall your study is important and well designed. I do believe, however, that it will conflict with the SUPPORT trial and would recommend that infants not be enrolled in both trials.
Regards
Neil Finer

-----Original Message-----
From: Debra Brandon [mailto:brand005@mc.duke.edu]
Sent: Wednesday, December 01, 2004 3:42 PM
To: nfiner@ucsd.edu
Cc: Ronald N Goldberg
Subject: Fw: Support Trial

Dr. Finer,

Sorry to be bugging you, but I know the support trial is hoping to get started after the first of the year. Have you had a chance to review my RO1 protocol and make a decision regarding dual enrollment.

Thanks,

Debbie Brandon RN, PhD, CCNS
Neonatal Program Director
Assistant Professor
919-681-3813 voicemail
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----- Forwarded by Debra Brandon/NurseSch/mc/Duke on 12/01/2004 03:47 PM -----

Debra Brandon/NurseSch/mc/Duke
11/10/2004 03:27 PM

To: nfiner@ucsd.edu
cc:
Subject: Support Trial

Dr. Finer,

We meet when you were at Duke to discuss the support trial. I mentioned to you the need to review my RO1 research protocol to ensure acceptability of dual enrollment between my study and the support study. I am not sure if you got a copy of my protocol from Kathy Auten. Mike Cotten is the chair of my DSMB and did not feel there should be a conflict.

ROP is included as a outcome in my study as a safety variable, but the cycled light intervention is not expected to have any effect on development of ROP. The was a remote risk of some unknown visual outcome because in my first study infants receiving near darkness longer appeared to develop ROP earlier than those infants receiving cycled light earlier (at birth or at 32 weeks PCA) (p=.08).

Please advise and feel free to call me as needed.

Thanks,

Debbie Brandon RN, PhD, CCNS
Neonatal Program Director
Assistant Professor
919-681-3813 voicemail
919-970(b) (6)pager

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prohibited. If you have received this email in error please notify the sender immediately.
(See attached file: IRB#4211-02-10 original.doc)

(See attached file: Cycled light - Duke.doc)

INTRODUCTION AND PURPOSE: Previous research on light exposure suggests that cycled light and continuous near darkness are both more beneficial in promoting health and development in preterm infants than continuous bright light (Blackburn & Patterson, 1991; Glotzbach et al., 1991; Mann et al., 1986; Miller et al., 1995). However, only recently has cycled light been compared to near darkness to ascertain which of these two is more beneficial for health and development (Brandon, 2000; Brandon et al., 2002; Miramin & Ariangno, 2000). Findings suggest that early cycled light is more beneficial than extended near darkness followed by cycled light, but it remains unclear at what gestational age cycled light should be initiated. The purpose of the proposed study is to determine the appropriate time for instituting cycled light for the youngest preterm infants ($\leq$ 28 weeks gestation at birth). A longitudinal randomized two-group design will be used to evaluate the effects of early (28 weeks) and late (36 weeks) cycled light on short- and long-term health and developmental outcomes including sleep-wake state development, weight gain, lung maturation, length of hospitalization (LOS), auditory and visual development, and neurodevelopmental outcomes.

BACKGROUND AND SIGNIFICANCE: The NICU light environment is one potential influence on developmental outcomes. Constant bright light has been related to an increase in infant respiratory instability (Shiroiwa et al., 1986) and less sleep and weight gain (Mann et al., 1986; Miller et al., 1995), consistent with findings on the negative consequences of constant light in the animal literature (e.g., Bellhorn, 1980). Light and visual stimulation are imperative for brain maturation and circadian rhythm development (Black, 1998; Rivkees, 2001; Rivkees & Hao, 2000; Torczynski, 1994), some light exposure in the NICU is inevitable, and cycled light is the typical environment after hospital discharge. However, the intensity and timing of cycled light that are best for preterm infants and the ways in which the light environment may affect later development, such as cognitive development, visual processing and attentional capabilities, are unknown.

The extent to which the fetal circadian system is mature is unknown (Rivkees, 1997), but the fetus clearly develops in a circadian environment with day-night differentiation. While the intrauterine environment is mostly dark, it is rich with circadian rhythm cues provided by the mother, such as sleep-activity, meal, and hormonal patterns; and the human fetus exhibits circadian rhythms in heart rate, respiratory rate, and adrenal steroidogenesis (Rivkees & Reppert, 1992; Seron-Ferre et al., 1993). Following preterm delivery, it is not possible to provide intrauterine circadian cues, but promotion of circadian rhythms is thought to be important to the health and development of preterm infants (Rivkees, 2001; Rivkees & Hao, 2000). Day and night cycling of light is clearly essential to the development of normal circadian rhythms (Rivkees, 1997) and it can be achieved with low intensity illumination (Rivkees et al., 1997). Exposure to cycled light after fullterm delivery is instrumental in the development of circadian rhythms (McGraw et al., 2000; Mirmiran & Kok, 1991; Recio et al., 1997). Preterm infants appear to have delayed maturation of circadian rhythms as compared to term infants (Kennaway, 2000; Kennaway 1996); and this late development of circadian rhythms may be related to lack of predictability and cycled light in the NICU environment (Mirmiran & Ariangno, 2000). Some light exposure in the NICU environment is inevitable, cycled light following hospital discharge is typical, and by 28 weeks the preterm infant retina may be mature enough to receive light and stimulate the SCN to promote circadian rhythms (Rivkees & Hao, 2000). Therefore, low intensity cycled light may be the best stimulus available to minimize the disruption of the maternal circadian rhythm environment.

DESIGN AND PROCEDURES: Settings. The clinical settings will be the intensive care nursery (ICN) and transitional care nursery (TCN) at Duke University Medical Center and the special care nursery (SCN) at Durham Regional Medical Center (described in Preliminary Studies). All infants will be recruited from the ICN, with the intervention continuing in the TCN and SCN. Follow-up assessments after discharge will be conducted in the Special Infant Care Follow-up Clinic (SICC) and Ophthalmology Clinic of the Duke McGovern-Davidson Children's Health Center (CHC). Preterm

infants born ≤ 28 weeks gestation are routinely followed in the SICC clinic at 9 and 18 months corrected age (CA) and in the ophthalmology clinic until at least 14 months corrected age.

Subjects. One hundred and forty infants born at < 28 weeks gestation will be enrolled over a period of 20 months. All recruitment will take place at Duke. Inclusion criteria include: < 48 hours of age or > 48 hours (up to 7 days) but still receiving photo-therapy (eyes are covered with eye pads), approval of the infant's physician, 23-28 weeks gestational age (assessed according to Ballard et al., 1991, standardized for infants < 28 weeks gestation), parental consent, cared for in incubator or bassinet, English speaking parents, and no history of known anomalies associated with neurological or visual problems (e.g., congenital glaucoma, Down Syndrome). With the use of only one infant from multiples, deaths, withdrawals, and loss to follow-up, it is anticipated that 100 of the 140 enrolled infants will be available for analysis. Based on power determinations this should be adequate for the weight gain, LOS, and key developmental hypotheses.

Intervention Groups. Neonates will be stratified according to birth weight ≤ 750 grams and > 750 grams to help ensure that the intervention groups are equal on this important covariate. The groups will be randomly assigned to one of two intervention groups: 1) early cycled light (28 weeks) (0-5 weeks of near darkness, 12-16 weeks of cycled light), or 2) late cycled light (36 weeks PCA) (8-13 weeks of near darkness, 4-8 weeks of cycled light). Continuous near darkness will be provided as 5-20 lux throughout the day except from 0630-0730 and 1830-1930, when lighting levels will vary based on nursing care needs at the change of shift. Near-darkness (5-20 lux) will be provided by using incubator (totally covered or with the front flap back) and bassinet covers and dimming individual bedside light during the day (0730-1830) and night hours (1730-0630). Cycled light will be provided in an 11-hour-on, 11-hour-off pattern. Daylight (200-300 lux) will be provided with the incubator cover folded on top of the incubator allowing light in from four sides, or with the bassinet cover off during day hours (0730-1830). With the daylight range of 200-300 lux and limited access to natural light, daylight can be ensured for infants in incubators and bassinets. In the nursery with natural light, the room lights will be used to maintain the standard light levels. On cloudy days the lux levels in the nursery do not exceed 300 lux, and on sunny days the nursery blinds will be used to block natural light as needed to maintain 300 lux. Near darkness will be provided as described above during night hours.

Descriptive and Covariate Variables. Selected demographic and illness-specific data will be obtained from the medical record when the infant is enrolled in the study and weekly during hospitalization. Illness specific data will be collected again after hospital discharge from the SICC medical record, and will include new diagnoses and re-hospitalizations. Demographic data will include birth weight, gestational age, gender, race, maternal age, maternal drug use, and maternal education. Illness specific data will include 1-minute and 5-minute Apgar scores, intraventricular hemorrhage stage, neonatal medical complications, medication history, infections, length of photo-therapy, day of life for the first feeding, length of time to reach growing calories without regression, and severity of illness as measured by the Score of Neonatal Acute Physiology (SNAP-I) (Richardson et al., 1993).

Outcome Variables. Outcome measures will include health indices (weight gain, LOS, hearing, development of ROP, visual acuity) and neurodevelopmental status (sleep-wake state development, neurological impairments, and cognitive, language, motor development). Short-term outcomes will be evaluated weekly, at 30, 33, and 36 weeks post-conceptional age (PCA), and at hospital discharge. Long-term outcomes will be evaluated at 9 and 18 months corrected age (CA). These time points were chosen because severe developmental problems are usually present by 9 months of age, and milder developmental delays, including language delays, are evident by around 18 moths of age (Vohr et al., 2000; Volpe, 1998). In addition, these time points are the typical evaluation points for infants returning to the SICC and are recommended by the NICHD Neonatal Research Network. Table 1 shows the data collection schedule for each outcome measure.

Hospital sleep-wake states will be measured utilizing a state-of-the- art infant sleep recording system. The infant's respirations and body movements will be recorded using a piezoelectric sensor pad placed under the crib pad, so that respiration regularity and respiratory pauses in each sleep state can be determined. Two electro-oculogram (EOG) probes will record rapid eye movements. The infant will continue on normal heart and apnea monitors. Twenty infants will be studied using both Holditch-Davis's (1990a) respiratory waveform and direct observation sleep-wake state measure and the PI's respiratory waveform and EOG sleep-wake state measure to establish reliability and validity of the respiratory waveform and EOG measure.

Table 1: Timing of Outcome Measures Including Repeated Measures

	Hospital Outcomes					Outpatient Outcomes						
Measures	Weekly in hospital	30 wks PCA	33 wks PCA	36 wks PCA	At discharge	4 mos CA_b	9 mos CA	12 mos CA	14 mos CA	18 mos CA	19 mos CA	24 mos CA
Short-term outcomes												
Sleep-Wake States		X	X	X								
LOS					X							
Hearing (BAER)					X, repeat after d/c with failure							
ROP Exams	X, bi-weekly, monthly							X				
Weight gain	X						X			X		X
Long-term outcomes												
Parent Sleep Diaries						X	X		X		X	X
Visual Acuity								X				X
Neuro Exam							X			X		
Bayley II							X			X		
REEL							X			X		

$_a$ PCA = post-conceptional age, $_b$ CA = corrected age $_c$ d/c discharge home

Procedures. Approval of the attending physician will be obtained prior to approaching families for consent. Families will be approached before delivery when mothers are hospitalized for bed rest or as soon as the mother has recovered from delivery and is available for informed consent. The project coordinator, a research assistant or an investigator will explain the study, allow time for questions, have a parent sign the consent form, and give a copy to the parent. The intervention will be initiated following group assignment and continue until the infant is discharged from the hospital. Incubator covers and bassinet covers are currently used in all three study nurseries.

RISK/BENEFIT ASSESSMENT: Potential benefits for study participation includes faster weight gain and earlier hospital discharge. In addition, there are potential benefits from study participation related to the additional monitoring that occurs with study subjects. The only risk, although remote, from receiving cycled light at 36 weeks PCA may be earlier development of retinopathy of prematurity (ROP) (Brandon et al., 2002). Development of ROP earlier in gestation did not result in an incidence of more severe ROP, but there may be some unknown visual risk. The only other remote risk is violation of confidentiality of a subject, since names and addresses of subjects must be maintained throughout the 24-month follow-up period.

SUBJECT IDENTIFICATION, RECRUITMENT, AND COMPENSATION: Approval of the attending physician will be obtained for all infants prior to approaching parents for consent. Mothers at risk for delivering preterm are often hospitalized prior to the initiation of labor for close monitoring and bed rest. Mothers hospitalized $\leq$ 28 weeks gestation will be approached antenatally for consent if the mother is medically stable (e.g., not in active labor or requiring intensive care). Other parents

will be approached for consent as soon as the mother has recovered from delivery and the parents are available for informed consent. The project coordinator, research assistant or an investigator will obtain consent for all subjects. The study will be explained, potential risks will be described, parents will be given time to ask questions, one parent will sign the consent form, and a copy of the consent form will be given to the parents. Following randomization of the infant to an intervention group, the parents will be informed of the intervention assignment and the intervention protocol for their infant.

Parents will be given $10 for every returned diary to compensate them for the burden of competing the diaries. Families will receive $25.00 and a valet parking pass to cover gas, parking, and food for each hospital visit for all surviving multiples regardless of study participation.

SUBJECT COMPENTECY: These subjects will not be competent to consent, either the mother or father will consent.

COSTS TO SUBJECT: N/A

DATA ANAYLSIS AND MONITORING: A data safety and monitoring board has been established as a requirement of the funding agency for all clinical research; members will include Dr. Michael Cotten, neonatologist and Duke IRB member, Richard Landerman, statistician, Diane Holditch-Davis, Professor, UNC School of Nursing and grant consultant, and Laura Enyedi, Duke pediatric opthalmologist. As the study statistician, Dr. Landerman will provide preliminary statistical analyses for the DSMB to review every 6 months. The board will meet in closed session and will have the authority to seek additional safety measures. Dr. Michael Cotton will chair the monitoring board. In addition, should any serious adverse event occur, the monitoring board will be informed immediately, and a special session will be scheduled to discuss strategies to deal with the problem.

In the preliminary study (Brandon et al., 2002), infants receiving cycled light at 36 weeks PCA experienced development of ROP earlier in gestation than infants exposed to cycled light at birth, but they did not have any differences in the severity of ROP. These findings are probably biased by very small sample size, which happened to include a few very premature infants who are ROP got severe. If dim illumination causes worse ROP, it goes contrary to our current scientific basis of ROP. In addition, a multicenter trial sponsored by NIH called LIGHT-ROP compared darkness to normal NICU lighting for preterm infants, hoping to find that decreased light caused less severe ROP found no differences in the incidence or severity between the near-darkness and the normal NICU light conditions. Since this study did not find that lower or higher light increased the severity of ROP, the risk for poorer ROP outcomes in this protocol are considered remote. However, ROP results and the other study outcomes will be monitored.

The monitoring board meeting will included a synopsis of protocol and design, discussion of the status of the intervention and data collection procedures, a summary of subject contacts, discussion of any adverse reactions or any potential adverse reactions, the status of data entry and verification, and a summary of any descriptive and inferential statistics to date. In addition, interim analyses comparing the two interventions will be conducted with special attention given to the auditory and visual outcome variables. The monitoring board will be given time to meet in closed session without the investigators to discuss the need for additional procedures to prevent adverse reactions or ensure data integrity and the unlikely case that the study may need an early termination due to unexpected adverse reactions or inadequate administration of the conduct of the study. Recommendations from the monitoring board meetings will be shared with the IRB and NIH during annual reports and immediately if the monitoring board identifies study related adverse events not previously reported or recommends early termination of the study.

Descriptive statistics will be calculated for all variables. Demographic and illness data from each group will be compared to assess group differences. Variables on which there are significant between-group differences will be entered as covariates in hypothesis testing. A statistician will supervise data analysis and monitoring.

CONFIDENTIALITY: To ensure confidentiality, subject numbers will identify subjects' files. All data will be stored in locked files under the direct supervision of the principal investigator.

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From:	Roy Heyne
To:	drfjcmd@aol.com; steichji@email.uc.edu; adusick@iupui.edu; golds005@mc.duke.edu; vjohnson@med.wayne.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; MPeralta@peds.uab.edu; adas@rti.org; petrie@rti.org; poo@rti.org; srhintz@stanford.edu; yvaucher@ucsd.edu; gary_myers@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; rdillard@wfubmc.edu; bvohr@wihri.org; richard.ehrenkranz@yale.edu
Cc:	JROSE@CareNE.org; JACKIE Hickman; bss5@cwru.edu; dkennedy@dmc.org; ldrichar@iupui.edu; mbball@leland.stanford.edu; Higgins, Rosemary (NIH/NICHD) [E]; lohme001@mc.duke.edu; ERavelo@med.miami.edu; pgallego@med.miami.edu; ellen_hale@oz.ped.emory.edu; VPhillips@peds.uab.edu; mcclure@rti.org; mary.j.brunner@UC.Edu; Teresa.Gratton@UC.Edu; mgfuller@ucsd.edu; diane_hust@urmc.rochester.edu; bjacksn@wfubmc.edu; lnoel@wihri.org; elaine.romano@yale.edu
Subject:	RE: FU Form Review Conference Call Thur Dec 2, 3-5pm ET (12-2pm PT)
Date:	Thursday, December 02, 2004 10:41:15 AM

Some comments on the proposed changes:

C.1. In the dichotomized form, the meaning is no longer as clear. Are we asking for whether anyone other than the caretaker contributes some additional support, and if so, whether that support is more than that provided by the caretaker? Are we including "in-kind" support, or just financial/income support?

C.4-5b Think the terminology here should be consistent with the revised wording in A.5.b, namely "other caretaker." Further qualifying this with the word "contributing" potentially mixes concepts of caretaking with "support".

E. The additional columns included in the expanded form do provide additional substance, though they will add to the interview duration. In the first column, regarding medical care, is the word "ongoing" meant to exclude one-time consults? Secondly, the 5th column ("If yes, received in past, but not now") may be redundant, since a "yes" answer to the prior column combined with a "no" answer to the following column should imply the child had received therapy in the past, but is not currently receiving. Speaking of which, I would suggest adding "still receiving" to the column "If yes, for how long." Regarding the "how often" need to clarify whether we are asking about current frequency, average past, or what.

Daycare/Child Care Service addendum: In the leading question, suggest adding "currently" to the opening question. Secondly, regarding the options that follow, need to be sure we are not counting the same hours of care under multiple options, i.e., the options should be mutually exclusive as far as care hours are concerned. Thirdly, I think a grid similar to the one under E above may work to capture this data, with columns such as "Type of Caretaker", "Relative: Y/N", "Caretaker Setting: Patient's Home, Other home, Center, etc.," "Average Days per week," "Average Hours/day". Finally, regarding the last question about sickness, I think the quantification and attribution required by this question will be difficult to obtain from parent recall and even more difficult to interpret.

>>> "Petrie, Carolyn" <petrie@rti.org> 12/1/2004 1:37:15 PM >>>
Suggested changes to the NF03 in addition to Dr. Bauer's comments, attached to this email.

Reminder for tomorrow's call:

Dear Follow Up PIs and Coordinators-

Thank you for your time and comments on the NF03 form earlier this week.
We are scheduling a two hour call to discuss the NF04 (first hour) and NF05 (second hour) since this time fit most schedules. Attached is the
list of variables collected and how often they are used for analyses.

Please send your comments and suggestions to the group if you are unable
to join the call.

For those of you attending, please write down you comments and provide evidence for your proposed changes. If there are larger issues that you
feel would require much discussion, email Dr. Vohr.

The call is schedule for

Thursday, December 2

3:00-5:00pm ET (12-2pm PT)

To join the call:

Dial Tollfree: 866-675(b) (6)

Passcode: (b) (6) when prompted)

Leader: Rose Higgins

Thank you!

Carolyn Petrie

Neonatal Research Network Coordinator

RTI International

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From: David Stevenson
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: MRI secondary study
Date: Tuesday, November 30, 2004 11:41:25 AM

Rose,

My vote is yes, unless I have to recuse myself.
David

At 06:14 AM 11/30/2004, you wrote:

> HI,
> Attached is a secondary protocol for SUPPORT from Susan Hintz to look at MRI and US to predict ND outcome. This study has been approved by the SUPPORT subcommittee and has been recommended for Steering Committee vote by the protocol review subcommittee. Please review this and send me a YES/NO vote based on the science of the study. If this is voted to go forward based on the science, I will immediately look for alternative sources of funding. There will be a later prioritization vote (as we recently had this past year) for funding. Please have your vote in by December 15, 2004. If you need a longer timeframe, let me know.
> Thanks!!
> Rose
>
> Rosemary D. Higgins, M.D.
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine NICHD, NIH
> 6100 Executive Blvd., Room 4B03B
> MSC 7510
> Bethesda, MD 20892
> (for Fed X use Rockville, MD 20852)
> 301-435-7909
>
> 301-496-3790 (FAX)

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: MRI secondary study
Date: Tuesday, November 30, 2004 10:59:11 AM

I vote yes
Neil Finer

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Abbot Laptook (E-mail) ; Carlo Waldemar (E-mail) ; Charles Rosenfeld ; Dale Phelps ; Ed Donovan ; Ehrenkranz Richard (E-mail) ; Jobe Alan (E-mail) ; Lemons Jim (E-mail) ; Michael O'Shea ; Michelle Walsh ; Neil Finer ; Oh William (E-mail) ; Poole Kenneth (E-mail) ; Ronald GOldberg ; Shahnaz Duara ; Shankaran Seetha (E-mail) ; Stevenson David (E-mail) ; Stoll Barbara (E-mail) ; Tyson Jon (E-mail) ; Walid Salhab (E-mail)
Cc: 'petrie@rti.org' ; Susan Hintz (E-mail) ; 'bkh@rti.org'
Sent: Tuesday, November 30, 2004 6:14 AM
Subject: MRI secondary study

HI,
Attached is a secondary protocol for SUPPORT from Susan Hintz to look at MRI and US to predict ND outcome. This study has been approved by the SUPPORT subcommittee and has been recommended for Steering Committee vote by the protocol review subcommittee. Please review this and send me a YES/NO vote based on the science of the study. If this is voted to go forward based on the science, I will immediately look for alternative sources of funding. There will be a later prioritization vote (as we recently had this past year) for funding. Please have your vote in by December 15, 2004. If you need a longer timeframe, let me know.
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301-496-3790 (FAX)

From:	Edward Donovan
To:	nfiner@ucsd.edu
Cc:	Edward Donovan; Higgins, Rosemary (NIH/NICHD) [E]; sduara@miami.edu; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu
Subject:	Re: SUPPORT
Date:	Monday, November 29, 2004 2:26:36 PM

Neil,

Help me interpret these data.
When I look at the 2 red columns in the table (slide 4), am I looking at the actual saturation? In this case, the difference is almost always 2.5 - 4.5%. This doesn't seem too bad. This is on a relatively flat portion of the O2-Hb dissociation curve - thus indicating a relatively large difference in pO2 and, likely a relatively large difference in fiO2.

What am I missing?
Ed

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

>>> "Neil Finer" <nfiner@ucsd.edu> 11/25/2004 10:30:43 AM >>>
Good Morning and Happy Thanksgiving to All

After the Turkey and the fun of the day
And when all the loved ones have gone away
Here's a little extra something for you to digest
And then we can all decide what we should do next!!

Be well
Neil

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD) [E]
Cc:	"Avroy A. Fanaroff, M.D."; "Betty Hastings"; "Ed Donovan"; "Ken Poole"; "Michele"; "Neil Finer"; "Shahnaz Duara"; "Wade Rich"
Subject:	FW: Compliance Monitoring
Date:	Friday, November 05, 2004 10:20:38 AM

Hi Rose
Here is a questionnaire. Please revise as you see fit.
Be well
Neil
Please answer the following questions regarding the SUPPORT Site Visit.
1. Did you find this visit helpful in preparing for the SUPPORT Trial?
Yes____ No ____
If Yes, Please indicate below the most useful aspects of the visit, and rank your answers from 1 - 5
1. Further explanation of the protocol to my staff ___
2. Allowed discussion with physicians regarding areas of the protocol that were of concern ___
3. Resolved areas of concern among the staff ____
4. Helped in an understanding of the practical aspects of the protocol - application of prongs, how to implement protocol etc ____
5. Improved understanding of the rationale for doing this trial ___

If No,
1. Please provide details of any issues or problems ie. Finer was a provocative fool!! Rich eats too much!
2. Were there areas that you feel should have been addressed that were not? If so please indicate these.
3. Was there adequate planning and did the time and place work for you and your staff?
If Not, please indicate why
4. What was the most useful aspect of this visit in your estimation?
5. Would you recommend site visits for other sites?

Many thanks
Neil Finer

----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
To: <nfiner@ucsd.edu>
Sent: Wednesday, November 03, 2004 1:07 PM
Subject: Re: Compliance Monitoring

> Neil
> Do you want us to develop a little survey to determine the value of
> the
site
> visits? This would be easy and we could ask all members who
> participated
at
> a given site to fill it out.

> Let me know
> Rose
> ----------
> Sent from my BlackBerry Wireless Handheld
>
>
> -----Original Message-----
> From: Neil Finer <nfiner@ucsd.edu>
> To: 'Edward Donovan' <Edward.Donovan@cchmc.org>; Higgins, Rosemary
> (NIH/NICHD) <higginsr@mail.nih.gov>; sduara@miami.edu
> <sduara@miami.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>;
> aaf2@po.cwru.edu <aaf2@po.cwru.edu>; mcw3@po.cwru.edu
> <mcw3@po.cwru.edu>; poo@rti.org <poo@rti.org>
> CC: wrich@ucsd.edu <wrich@ucsd.edu>
> Sent: Wed Nov 03 16:04:13 2004
> Subject: RE: Compliance Monitoring
>
> We are going to look at the first 5 patients enrolled at each site. In
> addition we have encouraged a buddy system. I am open to any process.
> I am traveling to Yale on Sunday. I think that the site visits have
> been very useful. Rose, it may be appropriate for you to discuss the
> value of the
site
> visits with actual sites that have had such a visit. Perhaps we should
> ensure that all Non- Committee sites are visited.
>
> Neil
>
>
>
> _____
>
> From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
> Sent: Wednesday, November 03, 2004 10:05 AM
> To: higginsr@mail.nih.gov; sduara@miami.edu; wcarlo@peds.uab.edu;
> aaf2@po.cwru.edu; mcw3@po.cwru.edu; poo@rti.org; nfiner@ucsd.edu
> Cc: wrich@ucsd.edu
> Subject: RE: Compliance Monitoring
>
>
>
> We need to discuss. We promised that we would call Coordinator and/or
> PI one day after enrollment for the first 5-10 subjects at each
> center. This might help some.
>
>
>
> Edward F. Donovan, M.D.
> Director
> Child Policy Research Center
> Children's Hospital Medical Center
> 3333 Burnet Avenue, ML 7014
> Cincinnati, OH 45229-3039
> Phone 513-636-0182
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> www.cprc-chmc.uc.edu
>

> >>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 11/03/2004
> 11:38:58 AM >>>
>
> Perhaps we could discuss this on a call. I think we simply just can't
tell
> people to be compliant, we need to determine early in enrollment
> whether
or
> not folks are adhering to the protocol.
>
>
>
> Discussion on this is appreciated!
> Thanks
>
> Rose
>
> -----Original Message-----
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Wednesday, November 03, 2004 10:59 AM
> To: 'Michele Walsh'; 'Carlo, Wally'; 'Duara, Shanaz'; 'Donovan, Edward
> (DONOVAEF)'; 'Fanaroff, Avroy'; Higgins, Rosemary (NIH/NICHD); 'Poole,
Ken'
> Cc: 'Wade Rich'
> Subject: RE: Compliance Monitoring
>
> Hi Michele
>
> I am aware of the Morris study as it was performed as a preliminary to
using
> adult ECMO. I am hoping that our protocol is simple enough that the
> actual intubation - extubation criteria can be explained in a single
> plasticized sheet on the infants bed.
>
> For Control-Surfactant infants these are Extubation Criteria only.
>
> For CPAP, I would hang the intubation criteria, and if the infant is
> intubated, then hang the extubation criteria or place both on the same
> sheet.
>
> We have also had difficulties in both multiple consents, and the need
> for oxygen. I am OK with doing the pilot on a child needing any oxygen
> - our problem has been room air.
>
> Be well
>
> Neil
>
>
>
>
> _____
>
>
> From: Michele Walsh [mailto:mcw3@po.cwru.edu]
> Sent: Wednesday, November 03, 2004 7:59 AM
> To: Finer, Neil; Carlo, Wally; Duara, Shanaz; Donovan, Edward

> (DONOVAEF); Fanaroff, Avroy; Higgins, Rose; Poole, Ken
> Subject: Compliance Monitoring
>
>
>
> Hi ALL;
>
> I want to raise a couple issues to consider for the main
>
> trial.
>
> 1. It seems to me that the success of the trial hinges on compliance
> with
>
> a possibly complex ventilation protocol at bedside. To my knowledge,
> compliance may have been a critical issue
>
> in at least two network trials. The first was SAVE where the CO2s
> didn't
>
> achieve separation, and the second was Glutamine where the majority of
>
> patients did not receive the intended 3 gm/kg/day of AA by day 3.
>
> Is there a way to enhance compliance with the protocol and document
>
> that decision making at the bedside in SUPPORT?
>
> I would encourage you to look at the ARDS trials which used a computer
>
> decision aid. I have attached one abstract here. Alan Morris, and
others,
>
> at Utah have pioneered the field of computer assisted decision making.
>
> Perhaps there is something we could learn from this approach to
> enhance
>
> the likelihood of compliance in SUPPORT.
>
> 2. We are having trouble finding patients for the oxygen pilot.
>
> One of the issues is the need for > 30% oxygen. Most of our patients
>
> are in < than this by 24 hours, yet many are still in some oxygen.
>
> Could we consider enrolling these patients on lower FiO2 in the pilot.
>
> We are also having trouble when approaching these parents after
phototherapy
>
> and Candida. ARe you also experiencing this? Michele
>
>

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Compliance Monitoring
Date: Thursday, November 04, 2004 12:23:58 PM

Sorry,I could not understand how winter of 2005 came before summer of 2005. Comes from being where there is no winter I guess.
Wade

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, November 04, 2004 9:03 AM
To: 'wrich@ucsd.edu'
Subject: RE: Compliance Monitoring

NO, hopefully it is this winter, 2005.
Thanks
Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, November 04, 2004 11:33 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: Compliance Monitoring

Should I assume you ment the announcement is in winter of 2004?
Wade

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 03, 2004 9:37 AM
To: 'wrich@ucsd.edu'
Cc: Neil Finer (E-mail)
Subject: RE: Compliance Monitoring

Wade and Neil - here is the current available information:

Thank you for your interest in the Neonatal Research Network (NRN). It is anticipated that there will be an announcement in winter 2005 for continuation of the NRN with an application due date of summer 2005. Peer review will occur in fall 2005 with council review in January 2006 and potential funding April 1, 2006. For more information about the NRN you can visit our website at http://neonatal.rti.org/. The approved concept for the NRN can be found at http://www.nichd.nih.gov/funding/funding_initiatives.htm.

The previous RFA for the current granting cycle (2001-2006) can be found at
http://grants2.nih.gov/grants/guide/rfa-files/RFA-HD-00-010.html.

Thanks again for your interest.

Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, November 03, 2004 12:29 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: Compliance Monitoring

Rose,

Neil would like to start looking at the data we need to collect when we re-apply. Are those forms available
to us to look at?
Wade

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 03, 2004 8:39 AM
To: 'nfiner@ucsd.edu'; 'Michele Walsh'; 'Carlo, Wally'; 'Duara, Shanaz'; 'Donovan, Edward (DONOVAEF)'; 'Fanaroff, Avroy'; 'Poole, Ken'
Cc: 'Wade Rich'
Subject: RE: Compliance Monitoring

Perhaps we could discuss this on a call. I think we simply just can't tell people to be compliant, we need to determine early in enrollment whether or not folks are adhering to the protocol.

Discussion on this is appreciated!
Thanks
Rose

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Sent: Wednesday, November 03, 2004 10:59 AM
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Be well
Neil

From: Michele Walsh [mailto:mcw3@po.cwru.edu]
Sent: Wednesday, November 03, 2004 7:59 AM
To: Finer, Neil; Carlo, Wally; Duara, Shanaz; Donovan, Edward (DONOVAEF); Fanaroff, Avroy; Higgins, Rose; Poole, Ken
Subject: Compliance Monitoring

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trial.
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We are also having trouble when approaching these parents after phototherapy and Candida. ARe you also experiencing this? Michele

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Compliance Monitoring
Date: Wednesday, November 03, 2004 12:41:54 PM

Rose
I am OK with a conference call. When will we hear from the DSMC? Perhaps we should plan a call after that?
Neil

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 03, 2004 8:39 AM
To: 'nfiner@ucsd.edu'; 'Michele Walsh'; 'Carlo, Wally'; 'Duara, Shanaz'; 'Donovan, Edward (DONOVAEF)'; 'Fanaroff, Avroy'; 'Poole, Ken'
Cc: 'Wade Rich'
Subject: RE: Compliance Monitoring

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> **To:** 'Michele Walsh'; 'Carlo, Wally'; 'Duara, Shanaz'; 'Donovan, Edward (DONOVAEF)'; 'Fanaroff, Avroy'; Higgins, Rosemary (NIH/NICHD); 'Poole, Ken'
> **Cc:** 'Wade Rich'
> **Subject:** RE: Compliance Monitoring
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> Neil
>
> ---
>
> **From:** Michele Walsh [mailto:mcw3@po.cwru.edu]
> **Sent:** Wednesday, November 03, 2004 7:59 AM
> **To:** Finer, Neil; Carlo, Wally; Duara, Shanaz; Donovan, Edward (DONOVAEF); Fanaroff, Avroy; Higgins, Rose; Poole, Ken
> **Subject:** Compliance Monitoring
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From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Compliance Monitoring
Date: Wednesday, November 03, 2004 12:29:46 PM

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From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 03, 2004 8:39 AM
To: 'nfiner@ucsd.edu'; 'Michele Walsh'; 'Carlo, Wally'; 'Duara, Shanaz'; 'Donovan, Edward (DONOVAEF)'; 'Fanaroff, Avroy'; 'Poole, Ken'
Cc: 'Wade Rich'
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To: 'Michele Walsh'; 'Carlo, Wally'; 'Duara, Shanaz'; 'Donovan, Edward (DONOVAEF)'; 'Fanaroff, Avroy'; Higgins, Rosemary (NIH/NICHD); 'Poole, Ken'
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Neil

From: Michele Walsh [mailto:mcw3@po.cwru.edu]
Sent: Wednesday, November 03, 2004 7:59 AM
To: Finer, Neil; Carlo, Wally; Duara, Shanaz; Donovan, Edward (DONOVAEF); Fanaroff, Avroy; Higgins, Rose; Poole, Ken
Subject: Compliance Monitoring

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We are also having trouble when approaching these parents after phototherapy and Candida. ARe you also experiencing this? Michele

From:	Wally Carlo, M.D.
To:	Edward Donovan; Higgins, Rosemary (NIH/NICHD) [E]; sduara@miami.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
Subject:	RE: FW: SUPPORT video
Date:	Tuesday, November 02, 2004 2:05:47 PM

Private

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Tuesday, November 02, 2004 10:16 AM
To: Edward Donovan; higginsr@mail.nih.gov; sduara@miami.edu; Wally Carlo, M.D.; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
Subject: Fwd: FW: SUPPORT video

What do you all think about this?

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

>>> "Petrie, Carolyn" <petrie@rti.org> 11/02/2004 10:37:03 AM >>>

Hi Ed- we thought we should check with you as well. I sent this email to Ken and Rose and would like your input. Carolyn

We are able to post the SUPPORT training video to our NRN website.
Where is the most appropriate place to provide the link? (eg private, public, front page, under SUPPORT protocol)

Thanks!
Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Wally Carlo, M.D.
To: Michele Walsh; Edward Donovan; Higgins, Rosemary (NIH/NICHD) [E]; sduara@miami.edu; aaf2@po.cwru.edu; nfiner@ucsd.edu
Subject: RE: oximeter alarms
Date: Tuesday, October 26, 2004 12:30:39 PM

I agree. I also agree with Michele that the specific monitor set up functions (e.g. alarm triggering or delay times as well as averaging times) can be changed to reduce alarms (particularly transient ones that have minimal to no clinical significance). These times may range from as short as 1 sec or as high as 30 seconds. We have lengthened some of these times to reduce alarms but have not studied this formally. Wally

---

From: Michele Walsh [mailto:mcw3@po.cwru.edu]
Sent: Tuesday, October 26, 2004 11:11 AM
To: Edward Donovan; higginsr@mail.nih.gov; sduara@miami.edu; Wally Carlo, M.D.; aaf2@po.cwru.edu; nfiner@ucsd.edu
Subject: Re: oximeter alarms

No I think you are correct- there will be alot of alarms,
unless the bedside clinician weans oxygen to move them
down farther into the target. This was a big issue for benchmarking.
We are trying to get some data on the number of alarms that
are produced by the use of the high sat alarm in the pilot here.
We also are doing an analysis of different sampling frequencies
and averaging times and their impact on the frequency of detected
desaturations. Regards, Michele

----- Original Message -----
From: Edward Donovan
To: Edward Donovan ; higginsr@mail.nih.gov ; sduara@miami.edu ; Wcarlo@peds.uab.edu ; aaf2@po.cwru.edu ; mcw3@po.cwru.edu ; nfiner@ucsd.edu
Sent: Monday, October 25, 2004 5:27 PM
Subject: oximeter alarms

I've been thinking about the oximeter alarms and clinician frustration if they are going off all the time.

Is this correct? If I keep me study baby near the upper target (92%) and my oximeter is "high reading", then the actual sat is often 95% or 1% below the upper alarm limit. It seems to me that, with the usual premie fluctuation, the alarm may be sounding frequently? The opposite would be true if I aim to keep the baby at 88% and the oximeter is "low reading".

Am I missing something?

Edward F. Donovan, M.D.
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www.cprc-chmc.uc.edu

From: Wally Carlo, M.D.
To: Edward Donovan; Higgins, Rosemary (NIH/NICHD) [E]; sduara@miami.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
Subject: RE: oximeter alarms
Date: Monday, October 25, 2004 7:45:32 PM

Yes, this is true but remember that alarms only go off at 84 and 96 for ALL babies, regardless of the group. So the effect you address is real! If you keep a baby at the limit of where he/she should be, alarms would go often which will help separate the groups. So my advice would be to tell the staff to try to keep babies in the middle of the desired range (88-92). Getting the babies to 90% sats should minimize the alarms, and this is desirable to optimize the separation. wally

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From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Monday, October 25, 2004 4:28 PM
To: Edward Donovan; higginsr@mail.nih.gov; sduara@miami.edu; Wally Carlo, M.D.; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
Subject: oximeter alarms

I've been thinking about the oximeter alarms and clinician frustration if they are going off all the time.

Is this correct? If I keep me study baby near the upper target (92%) and my oximeter is "high reading", then the actual sat is often 95% or 1% below the upper alarm limit. It seems to me that, with the usual premie fluctuation, the alarm may be sounding frequently? The opposite would be true if I aim to keep the baby at 88% and the oximeter is "low reading".

Am I missing something?

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From:	Susan Hintz
To:	richard.ehrenkranz@yale.edu
Cc:	Higgins, Rosemary (NIH/NICHD) [E]
Subject:	SUPPORT secondary
Date:	Thursday, October 21, 2004 5:45:43 PM
Attachments:	BudgetrevisedOct2004.doc Responses_to_Protocol_Rev.doc SUPPORT_neuroimaging.FINAL.doc

Dr. Ehrenkranz,

Attached, please find three documents pertaining to the revised SUPPORT secondary (my responses to the subcommittee's comments, the revised protocol, and the revised budget).

Thank you for your interest and the substantial time invested in reviewing these protocols.

Susan

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DRAFT ESTIMATED BUDGET: NEUROIMAGING SECONDARY TO SUPPORT
«GREETINGLINE», STANFORD UNIVERSITY REVISE

We have used 2003 data provided by RTI (see proposal, "Sample Size and power issues") to estimate the number of patients likely to be eligible for participation in this proposed secondary, and subsequently, the number of neuroimaging studies that may be performed. Survival to >7 days for 24 to 27+6 week EGA infants was 85%. Among those surviving >7 days, 82% survived to discharge. With the revised sample size for SUPPORT of 1310, this would result in approximately 1114 infants available for 7-14 day neuroimaging studies, and 913 infants available for 35-42 week neuroimaging studies.

1) Extent of participation in proposed secondary: It is understood that the extent of participation in this proposed secondary is not yet clear. Budgetary considerations may limit the extent of sites able to participate in the full secondary. In the most fiscally conservative situation, only those sites currently or soon to be performing routine brain MRI at near-term would obtain all neurodiagnostic studies. However, given the primary goal of this secondary (providing a safety arm to SUPPORT), it would be appropriate for all NRN sites to participate in early and late US collection. Since the publication of the neonatal neuroimaging practice parameter (Neurology 2002), it is likely that all NRN sites have implemented routine cranial US at 7-14 days and at near-term as standard of care. A survey of practices will be sent to Network PI's.

We have provided an estimate of absolute requirements, as well as possible enrollment scenarios.

2) Requirements for study, regardless of the level of participation in the proposed secondary:

- Cranial US central reading: This would include costs for shipping of films or CD's, coordinator time in collecting and preparing studies, and for radiologist(s) time to interpret both "early" (7-14 days) and "late (35-42 weeks) cranial US. If 80% enrollment for this cranial US portion were to be achieved, this would result in 891 "early" US and 731 "late US = 1622 studies.

- Conventional MRI central reading: This would include costs for shipping of films or CD's, coordinator time in collecting and preparing studies, and radiologist(s) time to interpret conventional 35-42 week MRI. Total number of studies would depend on the level of restriction of enrollment due to budgetary considerations.

Per Dr. Rosemary Higgins, radiologists AND RTI costs for central reading of ultrasounds = $15,000. I am estimating a similar cost for radiologist reading of MRI. The estimated cost for coordinator time for the PiNO study was $32/hr, with 5-6 hours/infant enrolled in PiNO. Thus:

Head US radiologists costs	$15,000
Brain MRI radiologsts costs	$15,000
Coordinator time = $32 x 5 hours x 891 infants	$142,560
TOTAL	$172,560

3) Costs for 7-14 day cranial US:
Because 7-14 day cranial US should be considered a "standard of care" routine in NICU's, no additional costs will be incurred apart from shipping/central reading as described above.

4) For centers with 35-42 week brain MRI already a "standard of care" routine":
If centers already performing MRI at near-term were to participate in the cranial US/MRI portion of the proposed secondary, *the additional cost of a 35-42 week cranial US would be the only additional cost incurred*, since those centers are unlikely to obtain both MRI and cranial US at near-term. Each network center will have a negotiated NIH reimbursement cost for each neuroimaging study; at Stanford, the negotiated cost of a cranial US is $210.29.

A survey of practices will be distributed to address how many Network centers *currently routinely* perform near-term brain MRIs.

5) For centers that do not routinely perform brain MRI at near-term:
If centers performing cranial US at near-term *were* to participate in the cranial US/MRI portion of the proposed secondary, *the additional cost of a 35-42 week brain MRI would be incurred*. At Stanford, the negotiated cost for a non-contrast brain MRI is $906.60.

However, if budgetary considerations were to prevent participation in the MRI portion of this secondary, these sites could participate in data collection with respect to cranial US findings. This approach would incur no additional neuroimaging costs for these sites.

Therefore, the total cost of additional neuroimaging for this proposed secondary will be dependent upon the proportion of enrolled patients requiring cost coverage for brain MRI vs. "late" cranial US. Each participating center will be required to submit a budget.

Scenario #1: The following are estimated costs for "late" US and conventional brain MRI based on 80% enrollment in the **full** neuroimaging study (731 patients), using Stanford negotiated costs, and assuming varying proportions of patients requiring cost coverage for brain MRI/cranial US as follows:

a) 10% of patients require brain MRI cost coverage/90% require "late" cranial cost coverage:

brain MRI cost	cranial US cost
0.1 x 731 = 73	0.9 x 731 = 658
76 x $906.60 = $66,181.80	658 x $210.29 = $138,370.82

Total cost for 35-42 week US/conventional MRI for this scenario: $204,552.62

b) 30% of patients require brain MRI cost coverage/70% require "late" cranial cost coverage:

brain MRI cost	cranial US cost

0.3 x 731 = 219	0.7 x 7 = 512
219 x $906.60 = $198,545.40	512 x $210.29 = $107,668.48

Total cost for 35-42 week US/conventional MRI for this scenario: $306,213.88

Scenario #2: Estimated costs for "late" US and conventional brain MRI based on limiting enrollment in the **full** neuroimaging study to 50% (457 patients), using Stanford negotiated costs, and assuming varying proportions of patients requiring cost coverage for brain MRI/cranial US as follows:

a) 10% of patients require brain MRI cost coverage/90% require "late" cranial cost coverage:

brain MRI cost	cranial US cost
0.1 x 457 = 46	0.9 x 457 = 411
46 x $906.60 = $41,703.36	411 x $210.29 = $86,429.19

Total cost for 35-42 week US/conventional MRI for this scenario: $128,132.55

b) 30% of patients require brain MRI cost coverage/70% require "late" cranial cost coverage:

brain MRI cost	cranial US cost
0.3 x 457 = 170	0.7 x 457 = 320
170 x $906.60 = $154,122.00	320 x $210.29 = $67,292.80

Total cost for 35-42 week US/conventional MRI for this scenario: $221,414.80

Scenario #3: Estimated costs for "late US" ONLY based on limiting enrollment to only those sites where brain MRI is currently or will be routinely undertaken for near-term imaging, using Stanford negotiated costs. The following are projections ONLY, since the total number of sites currently or soon to be performing routine brain MRI is not yet clear:

a) If 30% of the patients enrolled in SUPPORT would routinely undergo near-term brain MRI and participated in this secondary -

brain MRI cost	cranial US cost
$0	274 studies x $210.29 = $57,619.46

Total cost = $57,619.46

b) if 50% of the patients enrolled in SUPPORT would routinely undergo near-term brain MRI and participated in this secondary –

brain MRI cost	cranial US cost
$0	457 studies x $210.29 = $96,102.53

Total cost = $96,102.53

Scenario #4: Depending on budgetary considerations, it may be possible for SOME centers that are not currently performing routine near-term brain MRI to participate in this secondary. This involvement would be limited to highly motivated and interested sites, and would require reimbursement for MRI studies. An example of this would be the following:

If 30% of the patients enrolled in SUPPORT would routinely undergo near-term brain MRI and participated in this secondary, cost for those patients would be for cranial US only as shown above (Scenario #3 (a) = $57,619.46). If, in addition, 50 patients from highly motivated centers where MRI was NOT routinely performed at near-term wished to participate, the projected cost would be for MRI reimbursement = 50 x $906.60 = $45,330.00 (using Stanford negotiated costs as estimates). Thus, the total neuroimaging costs would be = $102,949.46

October 15, 2004

Responses to Protocol Review Subcommittee
Re: Neuroimaging and Neurodevelopmental Outcome: A SUPPORT Trial Secondary Study
From: Susan R. Hintz, M.D.

Dr. Ehrenkranz,

My thanks to you and the subcommittee for your careful and thoughtful review of the SUPPORT secondary proposal titled "Neuroimaging and Neurodevelopmental Outcome: A SUPPORT Trial Secondary Study". Below are responses to the subcommittee's August review of the proposal, and attached is the revised proposal. It is my hope that the subcommittee will now be able to be forwarded to the Steering committee for evaluation.

Responses to introductory comments:

I am very pleased that the subcommittee is enthusiastic about the changes to the protocol, specifically, that it is now linked with SUPPORT. I agree that this change makes it a "win" for both projects. In fact, many of the changes to the proposal were made after extensive discussion and evaluation of the important issues still to be addressed not only in this neuroimaging project, but in the SUPPORT trial as well. Thus, many of the alterations from the first draft to the subsequent revision noted by the subcommittee were made with those crucial issues in mind. Among those issues was the strong desire of many associated with the SUPPORT trial, to introduce a safety component with respect to neuroimaging findings. It is clear that this proposal provides a unique opportunity to fulfill that critical need. I agree with the subcommittee, however, that the wording of the abstract and the organization of the hypotheses unfairly subjugated the importance of the neurodevelopmental outcome component (see response below). Similarly, I agree with the subcommittee that the removal of the DTI component in the proposal is unfortunate, but reflects the current reality. It is clear that, after evaluation of the preliminary results of the Cranial Imaging Survey and discussion with several investigators, enormous obstacles to obtaining routine DTI exist in many sites. The subcommittee's review reflects an awareness and understanding of these problems.

Response to Point #1: The wording of the hypotheses

As noted above, I agree with the subcommittee that the continued importance of the neurodevelopmental follow-up component of this secondary appeared to be somewhat "buried" in the revised proposal. However, the critical importance of the short-term outcomes must also be emphasized, especially now that this proposal is linked with SUPPORT. I have therefore restated and restructured the abstract/introduction and hypotheses to again draw focus to the neurodevelopmental outcomes issues, and in concordance with the suggestions of the Protocol Review Subcommittee.

I also understand the concerns raised by the Subcommittee with respect to removal of the DTI component from the proposal. However, to include DTI as an "expected" component of this secondary proposal would be to deny the reality of the situation. DTI is not available in many Network centers, nor is implementation

anticipated. In centers where DTI is available, it is rarely performed routinely. Many Network investigators have voiced concerns that including DTI in a neuroimaging secondary would be prohibitive in terms of anticipated need for sedation (and thus ability to obtain consent), as well as with respect to cost and organization. However, this change to the protocol does not change the uniqueness and critical importance of the proposed study; structural MRI has not been studied on the scale or in the high-risk neonatal group proposed by this study. The results would be an important contribution to the literature. DTI could still be studied as well on a smaller scale, since we plan to submit an ancillary proposal covering investigation of the DTI parameters as discussed in the first proposal.

Response to Point #2: Importance of the early cranial ultrasound

The early ultrasound should already be performed routinely in all Network sites (recommended in "Practice Parameter: Neuroimaging of the Neonate", *Neurology* 2002), thus no additional cost would be incurred. The early ultrasound findings are an important component of the predictive modeling of neurodevelopmental outcomes. Our group at Stanford, and others, have compared the prognostic utility of early cranial imaging with later cranial imaging; however, times and types of neuroimaging have not been "standardized". The SUPPORT study presents a unique opportunity for a larger and better-defined evaluation. In cases in which more than one cranial ultrasound is obtained between 7-14 days, the study obtained closest to 14 days will be used. This statement has been added to the "Methods" section, within the "early cranial ultrasound" subsection.

Response to Point #3: Sedation

The issue of sedation, and how it will be presented in the consent form, will be left to the discretion of the investigator at each Network site. This issue was discussed in section F.3.b.ii.3 of the proposal ("Brain MRI: Sedation issues").

Response to Point #4: Cost of the secondary study

The majority of respondents (thus far) to the questionnaire did not know or did not indicate their center's NIH-negotiated costs for either cranial US or non-contrast brain MRI. Thus, a more "accurate" estimate in this regard cannot be made. Another call for completed questionnaires has been sent by email to Network investigators by RTI. However, the budget has been amended to include estimated radiologists and RTI central reading costs, as well as maximum coordinator costs (Please referred to Revised Budget). Dr. Higgins plans to approach other funding sources to determine the possibility of defraying study costs, but she cannot do so until this proposal is approved by the Steering Committee.

Response to Point #5: Cost-effectiveness study

I agree with Dr. Tyson that a cost-effectiveness study would need to be more clearly and completely designed. I have removed it from the secondary proposal, and will speak to Dr. Tyson separately about the feasibility of such an evaluation.

Response to Point #6: Central readers

I am acutely aware of the concerns held by the Subcommittee as it considers the possibility of central readers, coming on the heels of the numerous challenges of the

PiNO central reading. However, I believe there is a true need for central readers in this study. Furthermore, I do not believe that central neuroimaging reading will be as challenging as that faced by the PiNO study.

First, I agree with Dr. Tyson that pursuing central reading of only MRI studies, and not cranial ultrasounds, would be inappropriate. Nonetheless, it is likely that the level of comfort with brain MRI interpretation in term and near-term corrected age infants is not consistent across centers. Certainly, the level of comfort with cranial US interpretation is probably more consistent across centers since it is a frequently performed study. Therefore, the importance of central reading for brain MRI is clear, and the need for cranial ultrasound central readings logically follows. Second, the interpretation of the neuroimaging studies is central to the project. A corollary to this statement is that this project would represent the largest prospective collection of specifically timed structural brain MRI results among extremely preterm infants. Thus, the importance of "getting it right" cannot be underestimated, especially when it comes time to present our findings to the neonatology community. Finally, there are distinct differences between this central reading proposal and that of PiNO. We are prospectively defining that, at most, ONLY 3 studies will be interpreted for each subject in the SUPPORT trial participating in this proposed secondary. This is in contrast to the PiNO study, in which as many as 16 cranial ultrasounds per subject were read. Similarly, it is likely that the severity and unusual nature of abnormal findings will be less in the SUPPORT trial than in PiNO given the clinical condition of the patients.

My thanks again to the subcommittee for the significant time and effort you have invested. I believe that the revisions suggested by the subcommittee have resulted in a much improved proposal.

Susan R. Hintz, M.D.
Assistant Professor of Pediatrics
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Stanford University School of Medicine

Cc: Dr. Rosemary D. Higgins

Susan Hintz, Stanford University

NEUROIMAGING AND NEURODEVELOPMENTAL OUTCOME: A SECONDARY TO SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL (SUPPORT)

A. Abstract/Statement of Problem

Cranial ultrasound (US) is currently used for brain imaging in the extremely preterm population, but this modality cannot detect subtle brain injury that may be responsible for later neuromotor and cognitive delay. Magnetic resonance imaging (MRI) can identify brain structural abnormalities and white matter injury better than cranial US. The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) will evaluate if permissive ventilation strategies and lower SpO_2 targets will result in increased rates of survival without bronchopulmonary dysplasia (BPD) and survival without retinopathy of prematurity (ROP) among 24-27+6/7 week EGA infants. It is not known whether differing ventilation and oxygenation management approaches could lead to adverse consequences with respect to brain injury. Extremely premature infants are also at very high risk for neuromotor and neurodevelopmental impairment, with reported rates of cerebral palsy (CP) ranging from 11-20%, and of severe cognitive delay ranging from 30-60%. The power of MRI to predict neurodevelopmental outcome better than early and/or late cranial US among preterm infants is not yet known, but preliminary studies are promising. We therefore propose a secondary study in which specifically timed cranial US and brain MRI will be obtained. We will use neurodevelopmental follow-up data at 18-22 months corrected age to assess comparative and combined predictive capabilities of these neurodiagnostic modalities ("early" cranial US, "late" cranial US and MRI). We also will test the hypothesis that ventilation and oxygenation strategies described in SUPPORT will not be associated with an increase in death or brain injury (Grade 3/4 IVH by cranial US at 7-14 days or 35-42 weeks, abnormal brain MRI at 35-42 weeks). The NICHD Neonatal Research Network is uniquely positioned to embark upon such a project, which would be the first multicenter, prospective study to investigate these important questions.

B. Objective

We propose a secondary, prospective study of cranial US at 7-14 days ("early") and 35-42 weeks postmenstrual age (PMA) ("late"), and brain MRI at 35-42 weeks PMA among infants enrolled in SUPPORT to evaluate and compare the capabilities of MRI and early and late cranial ultrasound (US) to predict neuromotor and neurodevelopmental outcome at 18-22 months corrected age through development of predictive models. We also propose to determine if ventilatory or oxygen saturation interventions are associated with differences in the outcomes of death or abnormal neuroimaging findings (death/grade 3/4 IVH on "early" US, death/grade 3/4 IVH on "late" US, death/PVL, death/abnormal MRI).

C. Hypotheses

- Multivariate predictive modeling will show that abnormal findings on conventional brain MRI at 35-42 weeks postmenstrual age (PMA) will be more strongly associated with cerebral palsy and neurodevelopmental impairment at 18-22 months corrected age than abnormal findings on cranial US.

- There will be no differences in frequency of Death/Grade 3/4 IVH or Death/PVL on early or late US between Low and High SpO_2 groups, or between Early CPAP and Control ventilation groups
- The frequency of Death/abnormal findings on conventional brain MRI at 35-42 weeks postmenstrual age (PMA) will not be different between Low and High SpO2 groups, or between Early CPAP and Control ventilation groups.

D. Specific Aims

1) To obtain consistently performed, timed and interpreted neuroimaging studies in extremely preterm infants enrolled in SUPPORT:
    a. cranial US at 7-14 days of age
    b. cranial US at 35-42 weeks PMA
    c. MRI at 35-42 weeks PMA
2) To compare early and late US, and MRI findings between Low and High SpO_2 groups, and between Early CPAP and Control ventilation groups.
3) To utilize the NICHD Neonatal Research Network longitudinal follow-up programs to assess neurodevelopmental outcomes at 18-22 months corrected age, as described in SUPPORT.
4) To examine the independent associations of neuroimaging findings with neurodevelopmental outcomes through logistic regression modeling.
    a. Regression models would include traditional risk factors as covariates, with stepwise addition of the various neuroimaging modalities and findings, alone and in combination.
5) To develop models to estimate the prognostic utility of specific neuroimaging modalities and findings, alone and in combination, for neurodevelopmental outcomes.

E. Background, Significance and Rationale

The importance of an advanced neuroimaging component to SUPPORT:

SUPPORT will be the largest randomized controlled trial of ventilatory and oxygen saturation target management in extremely premature infants to date. Although the primary outcomes for the SUPPORT focus on survival without BPD and survival without ROP, it will be crucial to evaluate the potential impact of study interventions on both neuroimaging findings and neurodevelopmental outcomes. One possible concern could be that lower oxygenation parameters and less aggressive ventilatory management may be associated with a higher incidence of brain injury. This position might be extrapolated from early observations in preterm infants suggesting that intubation and mechanical ventilation decrease arterial blood pressure fluctuation and intraventricular hemorrhage (1), from reports correlating low estimated neonatal cerebral oxygen delivery with subsequent brain injury (2), or from studies of near-term and term hypoxic brain injury.

However, other investigations suggest that the opposite may be true; more aggressive ventilation strategies leading to hypocapnia may place the premature infant at higher risk for reduced cerebral blood flow (CBF) and subsequent white matter injury. This CBF-carbon dioxide reactivity observed in adult animals may be blunted or incomplete in newborn and preterm animals (3,4). Nevertheless, several clinical case

series of preterm infants have demonstrated strong associations of hypocapnia with significant abnormal findings on brain imaging and with adverse neurodevelopmental outcome (5-8), although other important risk factors were also identified.

At the very least, neuroimaging abnormalities in preterm infants are likely to be the result of a multifactorial process. Emerging evidence points to the unique vulnerability of the preterm infant brain in several respects. Low blood flow to the cerebral white matter and impaired cerebrovascular autoregulation in premature infants (9-11) may make subtle brain ischemic injury more likely. Coupled with this tendency to ischemic injury, is the vulnerability of developing oligodendroglial cells to damage (see below). Finally, it is possible that effects of exposure to *in utero* infection, frequently suspected in extremely preterm infants, may potentiate brain cellular injury caused by mild to moderate ischemia (12,13).

Summary: Given the interventions to be undertaken in SUPPORT, and the complexity and multifactorial nature of the development of white matter injury in the premature brain, advanced neuroimaging could be a critical safety component to the trial. This proposed secondary to SUPPORT would provide important additional information to investigators with respect to the impact of respiratory management on subtle brain injury.

The need to investigate emerging brain imaging modalities:

Premature infants are at high risk for neuromotor and neurodevelopmental impairment. Recent reported rates of cerebral palsy (CP) at 18-24 months corrected age range from 11-20%, and of cognitive delay range from 30-60% for the extremely low birth weight (ELBW) population (14-16). Yet, despite numerous investigations, the causes for these impairments remain unclear. Correlation of specific neonatal factors, particularly neuroimaging findings, with adverse neuromotor and neurodevelopmental outcomes are frequently, but not consistently demonstrated. Many studies have emphasized the association of cranial US abnormalities including intraventricular hemorrhage (IVH) grades 3 and 4, periventricular leukomalacia (PVL) and ventricular dilatation with subsequent neurologic and cognitive impairment (14-20). Most investigators have found abnormalities on cranial US to be an independent risk factor for neuromotor abnormalities, but not necessarily for cognitive impairment.

But, the finding of severe cranial US abnormalities is not uniformly predictive of adverse neuromotor outcome in the premature population. In a study of perinatal correlates of neurologic impairment at 18-22 months corrected age among VLBW infants (20), only 52% of the infants with CP on follow-up had had severe cranial US abnormalities. This finding was in contrast to a 12% rate of severe cranial US abnormalities among matched controls without CP. In a neurodevelopmental follow-up study of ELBW infants in a multicenter, double masked, randomized controlled trial of indomethacin prophylaxis in preterms (TIPP), rates of survival without neurosensory impairment were found to be similar between treatment groups although incidence of grade 3 or 4 IVH on cranial US had been significantly reduced by treatment with indomethacin (21).

Smaller studies have investigated the capabilities of cranial US at term to predict CP among preterm infants, revealing that the sensitivity of this diagnostic tool is only approximately 60% (22,23). Other reports have indicated that cystic PVL may be

detected in infants without previous cranial US abnormalities at several months of age (24-26). These studies suggest that only certain types of brain injury may be detectable with cranial US, and that timing of studies may be crucial. Furthermore, the radiologic changes associated with PVL may be visible by US only at a particular point in time; if cysts do not form as a result of injury leading to PVL, it may not be visible by US. Thus, injury could have occurred but would not be detected by US.

Summary: Cranial US, the imaging modality currently considered to be standard of care, may not be sensitive enough to detect brain injury that is responsible for later neuromotor or neurodevelopmental delay among ELBW infants.

MRI compared with cranial US to assess of brain injury and predict neurologic outcome

MRI provides a more complete and anatomically detailed evaluation of the neonatal brain. Several studies have compared the relative capabilities of US and MRI to detect brain injury among preterm infants in the newborn period. These reports concluded that MRI detects white matter injury better than HUS (27-29), and provides additional information regarding hemorrhage and cystic changes not noted by cranial US. Childs, et. al. assessed MRI and serial cranial US in both preterm and term infants, and concluded that MRI was more sensitive in identifying periventricular white matter lesions (30). However, neurodevelopmental outcome of the infants in those studies were not reported.

Few studies have compared MRI with cranial US in terms of their capabilities to predict neurodevelopmental outcome among premature infants; those are small, primarily single-center efforts. Furthermore, due to variability of timing, of imaging, and differences in MRI scoring and interpretation, the studies are difficult to compare. Valkama, et. al. (31) assessed MRI compared with cranial US performed at term in 51 VLBW, preterm infants (<34 weeks). Twelve infants were diagnosed with CP at 18 months corrected age. MRI parenchymal lesions predicted CP with 100% sensitivity and 79% specificity whereas US at term predicted CP with 67% sensitivity and 85% specificity. The authors concluded that MRI was the more reliable methodology. Stanford University researchers (see below "Preliminary Studies and Results") have completed a prospective study of neuroimaging among VLBW, preterm infants with neurodevelopmental follow-up at 18-22 months and 30 months corrected age (32). The group demonstrated that MRI at term predicted CP with superior sensitivity and positive predictive value to early cranial US.

Other studies have suggested the potential prognostic advantages of MRI compared with cranial US. Roelant-van Rijn and colleagues (33) studied 61 preterm infants with cranial US, and MRI within the first weeks of age and/or at term. MRI at term was found to be helpful in delineating internal capsule abnormalities, which was considered to be useful in predicting later hemiplegia. Other preliminary reports include that of Austin, et. al. (34) in which 93 VLBW infants evaluated with brain MRI at term underwent neurodevelopmental assessments at one year corrected age. White matter injury on MRI at term was correlated with neuromotor abnormalities such as hypertonicity, hypotonicity, and motor delay. In a very small group of premature infants <36 weeks, Miller, et. al. (35) showed that cerebellar hemorrhages detected by MRI, even if not

associated with white matter injury, appeared to be associated with adverse neurodevelopmental outcome at 12 months.

There are potential criticisms to these studies. In most cases, MRI was compared with only "late" cranial US or only "early" US; a more complete comparison would include both early and late cranial US, demonstrating that the design of neuroimaging collection strategies in prospective studies is crucial. Many studies focus narrowly on neuromotor outcome, specifically incidence of CP as outcome variables. A broader neurodevelopmental assessment and comparison is warranted. Finally, all studies of MRI findings and correlation with neurodevelopmental outcomes in preterm infants thus far are small; it is therefore not possible to draw powerful conclusions, especially with regard to ELBW patients. In fact, the recently published "Practice Parameter: Neuroimaging of the Neonate" (36) failed to definitively recommend routine MRI for VLBW preterm infants in part due to the lack of follow-up studies. But, many of the reports reviewed above were not available during the development of the "Practice Parameter".

Summary: Studies to date suggest that MRI may be a more powerful tool in predicting adverse neuromotor outcome among preterm infants. However, timing of studies vary between published reports, and very few prospective neurodevelopmental follow-up investigations have been undertaken to assess the comparative prognostic capabilities of these neuroimaging techniques for neuromotor and cognitive outcomes.

The importance of subtle white matter injury

Periventricular leukomalacia (PVL) has been categorized as "focal" and "diffuse" (37,38). Focal PVL has been described as the result of severe ischemic-necrotic injury and is located deep in the white matter. This type of injury may lead to the development of cystic changes or significant findings that can be detected by cranial US or conventional MRI. Diffuse PVL is the result of less severe injury, diffusely located in the white matter. The mechanism for diffuse PVL may be multifactorial, including: 1) mild to moderate ischemia due to decreases in cerebral blood flow consistent with impaired autoregulation, 2) vulnerability of immature oligodendroglial cells to ischemic injury and damage by chemical mediators, and 3) oligodendroglial cell susceptibility to injury and death after intraventricular hemorrhage due to creation of oxygen free radicals. The sensitivity of the immature oligodendroglial cells to cytokine-induced injury may help to provide a pathophysiologic explanation to the observations of increased CP rates among infants born to mothers with chorioamnionitis, and among infants with early sepsis.

Diffuse PVL may be a clinically important and prevalent white matter injury in the preterm infant. Yet, diffuse PVL is unlikely to be seen by cranial US. Diffuse PVL may also be challenging to detect reliably on conventional MRI. However, in a study by Counsell et. al. (39), diffuse excessive high signal intensity (DEHSI) in the white matter of preterm infants at near-term was associated with higher apparent diffusion coefficient values on diffusion weighted MRI. This finding suggested that subtle injury, causing changes in cellular differentiation and probable preferential death of preoligodendrocytes, resulting in diffuse PVL (40), may be structurally visible in the form of DEHSI. The developmental significance for the preterm infant is not known. It is also

important to note that all subtle white matter injury is unlikely to be detectable even by MRI.

Summary: IVH and focal cystic PVL are detectable by conventional MRI or even cranial US. However, more subtle factors and injuries may lead to oligodendroglial cell death and diffuse PVL. Diffuse PVL is not likely to be detected by cranial US, but might be detected by MRI. Such injury may have a substantial impact on normal white matter development and neuromotor outcome in the preterm infant; however, this question has been poorly studied in a large-scale, prospective manner.

Preliminary Studies and Results

A coordinated effort among neonatologists, radiologists, engineers, technicians and developmentalists has been in place at Lucile Salter Packard Children's Hospital and the Lucas Center for Nuclear Magnetic Resonance at Stanford University since the late 1990's. The objective of this group has been to combine the talents and expertise from various fields of science to investigate novel, potentially clinically relevant neuroimaging approaches in term and preterm infants. As a result, a strong infrastructure exists to allow for the development and implementation of further prospective studies and trials of MRI and DTI in the neonatal population.

Cranial US vs. conventional MRI for prediction of CP in VLBW infants: Infants of <1250 grams and <30 weeks EGA were enrolled a prospective observational study of the capabilities of early cranial US compared with conventional MRI at near-term to predict CP at 18-22 months corrected age, and 30 months (32). Cranial US was obtained twice during the first two weeks of life, and the most abnormal findings were used for analysis. Conventional MRI and cranial US were scored with respect to size of hemorrhage, parenchymal involvement, and ventricular dilitation. 62 infants participated in the study, with one excluded from analysis due to a later diagnosis of muscular dystrophy. The sensitivity and specificity of near-term MRI for predicting CP at 18-22 months were 71% and 91% respectively. The sensitivity of MRI for predicting CP at 30 months of age increased to 86% with the specificity remaining high at 89%. Although the specificity was comparable to MRI, the sensitivity of US to predict CP was only 29% at 18-22 months and 43% at 30 months. The positive predictive value of US was 22% at 18-22 months and 33% at 30 months.

This study, one of the largest prospective comparative neuroimaging studies of VLBW infants and neurodevelopmental outcome, supports the suggestion that conventional MRI may be superior to cranial US with respect to prediction of neuromotor abnormalities. There are limitations to this study, however. Comparison cranial US were performed early in the hospital course (<2 weeks), and no US contemporaneous with the MRI were routinely obtained. Recent studies by other investigators have also determined that, among VLBW infants, early cranial US poorly predicts non-cystic white matter injury on MRI at term (41). Also, previous reports by Valkama, et. al. (31) suggest that cranial US at term was a substantially less sensitive predictor of CP than MRI at term. Nevertheless, a thorough comparison would include early and later cranial US determinations to evaluate the potential combined prognostic power of early and late cranial US compared with MRI at term. In addition, this study

was significantly limited by small sample size, with only seven infants diagnosed with CP on neurodevelopmental follow-up. Sample size considerations also restricted possibilities for multivariate modeling of outcomes, and meaningful analysis of Bayley Scales of Infant Development II scores. All of these limitations could be addressed in the proposed prospective multicenter study.

F. Research Design and Methods

1. Study Design: This proposed secondary to SUPPORT is a prospective study of traditional (cranial US at 7-14 days and 35-42 weeks PMA) and advanced (MRI at 35-42 weeks PMA) neuroimaging with respect to SUPPORT randomized ventilation and oxygen saturation interventions. The capabilities of these neuroimaging modalities to predict neurodevelopmental outcome at 18-22 months corrected age will also be assessed.

Perinatal, demographic and neonatal data will be collected as part of the ongoing NICHD Neonatal Research Network Survey of Morbidity and Mortality Among VLBW Infants (401-1500g) for the purposes of the study. Cranial US will be obtained at 7-14 days and at 35-42 weeks PMA. *Clinical* interpretation of cranial US will continue to be performed at individual Network sites, but for purposes of research outcomes, cranial US should ideally be interpreted by central readers. Brain MRI will be obtained at 35-42 weeks PMA; MRI will be interpreted by a central reader(s) for purposes of research outcomes, but clinical interpretation will be performed at individual Network sites. Detailed neuromotor and neurodevelopmental examinations will be undertaken at 18-22 months corrected age as part of the NICHD Cooperative Multicenter Network of Neonatal Intensive Care Units: Follow-Up of ELBW Infants (401-1000g), and per SUPPORT protocol.

Statistical analysis will include bivariate analyses, and logistic regression modeling to 1) assess the association of SUPPORT ventilation and oxygenation randomized treatment groups with neuroimaging, 2) evaluate the strength of independent associations of specific neuroimaging findings with neurodevelopmental outcomes and 3) develop predictive models.

2. Study Population

Inclusion Criteria

- Enrolled in the NICHD Neonatal Research Network SUPPORT study
- Cranial ultrasound can be obtained at 7-14 days of age and at 35-42 weeks PMA
- Brain MRI can be obtained per study specifications (see Appendix D) at 35-42 weeks PMA

Exclusion Criteria

- Patient likely to be discharged or transferred from the Network center with MRI capability by 35-42 weeks PMA.
- Patient unlikely or family unwilling to participate in neurodevelopmental assessment at 18-22 month corrected age
- Presence of known or suspected congenital anomalies including:
  - ➤ Chromosomal anomalies
  - ➤ Complex congenital heart disease (PDA, small muscular VSD or PFO are NOT considered to be congenital heart disease for the purposes of this study)

- ➤ Congenital infection (TORCH, untreated maternal HIV, syphilis)
- Prior enrollment in conflicting clinical trial
- Lack of informed consent

Enrollment of Subjects

Screening: Each center will be responsible for devising a screening strategy to identify all potential participants using the study inclusion and exclusion criteria. Screening and identification of patients should take place by 14 days of age since the "early cranial US" must be performed at 7-14 days.

Informed consent: Each participating center will follow procedures for developing informed consents as set out by the local Institutional Review Board (IRB). It is expected that the parents of all eligible infants will be approached to participate in this prospective study, and informed consent must be obtained by the individual center.

Eligible infants not enrolled: The reasons for non-enrollment of eligible infants will be documented. Short- and long-term outcomes of eligible infants not enrolled in this study will be documented as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality in VLBW Infants (Generic Data Base (GDB)) and, if enrolled, as part of the ongoing NICHD Neonatal Research Network ELBW neurodevelopmental follow-up study.

No MRI obtained for enrolled infants: An important objective of the proposed study requires acquisition of MRI at 35-42 weeks PMA; it is important that each participating center make this a priority. However, it is understood that if the patient is deemed medically unstable (Appendix B) during the entire 35-42 week PMA period, an MRI will not be obtained. Other reasons for inability to obtain the MRI will also be documented.

3. BASELINE DATA, NEUROIMAGING, NEURODEVELOPMENTAL FOLLOW-UP

a. Baseline Data: Perinatal, demographic and in-hospital variables

i. INTRODUCTION AND FEASIBILITY: This secondary protocol will not require substantial data collection in addition to that already in place at participating centers; nor will it mandate patient management. The data collection instruments will be those already in routine use in the participating centers through the NICHD Neonatal Research Network Survey of Morbidity and Mortality in VLBW Infants. These data are obtained through the use of "Generic Data Base forms" which allows for consistent accrual of demographic, perinatal and neonatal variables among this high-risk population.

ii. METHODS: Research nurses at participating centers will collect data using the standardized Generic Data Base Forms NG02, NG03, NG05 and NG07, and the definitions detailed in the Manual of Operations. Perinatal, demographic and in-hospital data collected will be from those data collection instruments. Additional queries will attempt to delineate the potential independent contribution of hypotension and hypocarbia, purported to be causes of cerebral hypoperfusion (42-46) leading to diffuse or focal neonatal brain injury, to abnormalities on MRI and DTI. These questions will be coordinated with the SUPPORT protocol subcommittee and focus on 1) need for pressors and 2) the degree of hypocarbia experienced

Since these infants will be participating in the SUPPORT trial, information regarding ventilation strategy and oxygen saturation randomization arms will also be included in neurodevelopmental outcomes models as additional factors.

b) Neuroimaging studies

i. INTRODUCTION AND FEASIBILITY: Changes in the approach to neuroimaging may be required for implementation of this research protocol at participating centers; the extent of the changes will depend upon the procedures already in place at each individual center. Within the Neonatal Research Network, cranial US should already routinely be performed in ELBW infants 7-14 days of age window, and are frequently performed at near-term. For the purposes of this study however, central neuroimaging readers should ideally be secured for both early and late cranial US since disparate interpretations of would potentially complicate analysis.

A brain MRI at near-term is part of the routine VLBW infant care protocol in some of the Network centers. A survey will be sent to Network PI's respect to extent of this practice is pending. However, because this diagnostic approach is emerging, and due to the current lack of standardized grading systems, MRIs must be interpreted by central pediatric neuroradiologist readers.

Network centers with devices capable of performing neonatal conventional brain MRI (4 mm slice, 0 gap) could participate in the MRI portion of this proposed study. Due to budgetary considerations, it is possible that implementation of this proposed secondary may be limited only to selected Network sites. The most conservative approach would be that only those sites in which MRI is currently, or will soon be, implementing routine near-term MRI will participate in this proposed secondary.

ii. METHODS:

1) "Early cranial ultrasound": A cranial ultrasound will be obtained at 7-14 days of age. If more than one cranial ultrasound is obtained during that time period, the ultrasound obtained closest to 14 days will be used. Results will be interpreted as indicated in the Manual of Operations (See Appendix C), and reported in the NG03 form, but central readers will formally interpret ultrasounds.

Although not currently *required* within the parameters of the NICHD Neonatal Network VLBW Registry, recent ELBW neurodevelopmental follow-up studies from the NICHD Neonatal Research Network reveal that virtually all of these extremely high risk infants surviving to the 18-22 month visit have had at least one cranial US early in the course of their hospitalization. Furthermore, the "Practice Parameter" for neuroimaging in the neonate recommends *screening cranial US should be performed on all infants with EGA of <30 weeks at 7-14 days of age* (36); it is likely that Network centers have already implemented this practice to patient care protocols.

2) "Late cranial ultrasound": A cranial ultrasound will be obtained at 35-42 weeks PMA, and within 7 days of brain MRI. All late cranial US will be reported in the NG03 form as indicated in the Manual of Operations (See Appendix C), and will ibe interpreted by central readers.

Late cranial US is not currently required in the Network paradigm; however, the importance of this later exam to the completeness of the proposed study is clear. Also,

the "Practice Parameter" as referred to above (36) recommends that *cranial US should be optimally repeated at 36-40 weeks' postmenstrual age*, so it is likely that many
3) Brain MRI: A brain MRI will be obtained at 35-42 weeks PMA, and within 7 days of the "late cranial ultrasound". Images will be acquired as described in Appendix A. Conventional MRI images will be transferred to Stanford University for interpretation and scoring by central pediatric neuroradiologist reader(s) (Patrick Barnes, M.D., and others as suggested by the Steering Committee) who will be masked to any unique patient identifiers and to patient history and outcome. Dr. Barnes is a highly regarded, widely published pediatric neuroradiologist with extensive experience in the field of MRI, MR spectroscopy, diffusion weighted and diffusion tensor imaging. In addition to his dedicated work at Stanford University, Dr. Barnes has also collaborated with researchers such as TE Inder, PS Huppi and JJ Volpe. Dr. Barnes is an expert in the timing of fetal and neonatal brain injury using methods such as MRI and MRS.

MRI interpretation and data access: Conventional MRI images will be interpreted and scored by a central neuroradiology reader (Appendix C). The central reader(s) will be responsible for completion of data forms and data transfer to the Network Data Center. Each participating center is expected to counsel families with regard to MRI findings on the basis of its own neuroradiologist's interpretation of the images.

Sedation issues: MRI studies are performed without sedation at Stanford University. Patients are imaged following a feeding, ear plugs (MiniMuffs, Natus) are used to reduce the noise by up to 50% and patients are bundled to preserve warmth, maintain sleep and reduce patient motion. Of the 14 sites that responded to an earlier NICHD Neonatal Research Network Brain Imaging Survey (Dr. Seetha Shankaran), five indicated that they already use sedation for MRI. Another six sites indicated that sedation is used if clinically necessary. One site responded that sedation is not used. Responses from two centers were not clear. At Stanford, the approach of "feeding and swaddling" has yielded successful conventional MRI imaging with excellent quality in almost all cases. Sedation, if needed, would clearly increase the likelihood of obtaining a high quality scan. Network centers in which sedation is standard of care, and MRI is routinely performed, should certainly be able to continue their current approach. Although several of the sites have already indicated that sedation is used routinely, it is appreciated that the use of sedation in the context of a research protocol may make IRB approval more difficult. One possible solution for centers with such challenges would be to present two consent forms: the first for participation in the study itself, indicating that "feeding and swaddling" methods would be tried; the second, for consent to use sedation if this conservative approach were not successful, or if it is considered medically inadvisable to implement the "feeding and swaddling" approach (i.e., severe reflux). Clearly there are differing approaches to sedation for MRI studies, thus the issue of sedation will be left to the individual investigators at each Network site.

c) Neurodevelopmental Follow-up

i. INTRODUCTION AND FEASIBILITY: Neurodevelopmental follow-up for ELBW infants is already a focused objective within the NICHD Neonatal Research Network; all Network centers have complete neurodevelopmental assessment teams and patient tracking infrastructure in place. In addition, neurodevelopmental follow-up is already a part of SUPPORT protocol.

ii. METHODS: Follow-up visit will be conducted at 18-22 months corrected age as described in the "NICHD Neonatal Research Network ELBW Follow-Up Study Manual of Operations" (see Appendix C). An exam for neurological exam for cerebral palsy will be performed. The Bayley Scales of Infant Development (Bayley N. Bayley Scales of Infant Development-II. San Antonio, TX: Psychological Corporation; 1993) will be administered by a Bayley Examiner certified for the Follow-Up Study. In addition to neurodevelopmental assessments, information regarding socioeconomic status, level of education of the primary caregiver, and marital status is routinely obtained at the 18-22 month visit.

4. STATISTICAL CONSIDERATIONS

Outcomes:

Primary outcomes considered will include

- Death/Grade 3/4 IVH on 7-14 day cranial US
- Death/Grade 3/4 IVH on 35-42 week cranial US
- Death/PVL on 35-42 week cranial US
- Death/abnormal MRI at 35-42 weeks

Secondary outcomes will include

- cerebral palsy
- BSID MDI<70
- BSID PDI<70
- Neurodevelopmental impairment (NDI) defined as any of the following: deafness, blindness, moderate-severe cerebral palsy, or BSID II MDI or PDI score <70.

Bivariate analyses: Analyses of frequency of primary outcomes with respect to SUPPORT treatment groups will be undertaken. Comparisons will be made between ventilation strategy groups (Early CPAP and Control groups) within each randomized oxygenation group, and between oxygenation strategy groups (Low and High SpO2) within each randomized ventilation group. Continuous measures will be compared using the Student t-test and ANOVA where appropriate, and Chi-square analysis will be used to compare categorical data. These analyses would also adjust for the clustering effect introduced by randomizing by week of study.

Sample size and power issues:

Overall GDB and follow-up patient numbers: For year 2003, 1468 infants 24+0 to 27+6 weeks EGA were enrolled in GDB. Of those, 1249 survived to >7 days and 1209 survived to >=14 days. 1027 patients survived to hospital discharge. In year 2003, a total of 725 former 24+0 to 27+6 week EGA patients completed neurodevelopmental assessment at 18-22 months corrected age.

Frequency of neuroimaging outcomes:

Ultrasound: For year 2003, among infants 24+0 to 27+6 weeks EGA surviving to >=14 days, the frequency of Grade 3/4 IVH on cranial US was 20.3%; for those surviving to discharge it was 18.6%. The frequency of PVL among those surviving to discharge was 3.9%.

MRI: "Abnormal" conventional MRI results among preterm infants at near term are much more difficult to quantify. This is due both to a paucity of available data in the literature, and disparate methods of reporting and scoring "abnormalities" on brain MRI among preterm infants. Two recent studies have attempted to estimate the frequency of white matter signal abnormality, as well as other abnormal findings. Inder and colleagues (47) reported on findings of brain MRI performed at term equivalent age in 100 infants of 23-32 weeks EGA. Only 36/100 were considered to have no white matter signal abnormality, whereas 16/100 had extensive severe white matter signal abnormality. Cortical gray matter abnormalities were rare, with 96/100 patients categorized as normal. Lateral ventricle size was normal in only 40/100. Miller, et. al. (48) reported on MRI findings of 32 consecutive preterm infants, but imaging was performed at earlier postconceptual ages. In addition, previous studies by Maalouf (27) found that 12/19 (63%) preterm infants studied by MRI at 38-44 weeks PCA had abnormal white matter signal, but of those only 7 were moderately to severely abnormal (37%). Childs (30) found 29 of 105 preterm infants (<37 weeks) had abnormal periventricular white matter on MRI, and an additional 5 infants with other abnormalities (32% abnormal). However, the age at the time of MRI in that study ranged from 1-42 days, and PCA at time of scan was not reported. Counsell, et. al. found that, among preterm infants at near term, 34 of 50 had "overt" white matter abnormality or diffuse excessive high signal intensity white matter abnormalities (68% abnormal) (39). In summary then, the frequency of "abnormal" brain MRI in preterm infants ranges from 32-68%. One projected benefit from this proposed secondary study, in fact, would be that the frequency of specific MRI abnormalities in a large premature group could be better clarified and described. For the purposes of sample size and power calculations for this proposal, a conservative estimate of 40% white matter abnormality by MRI at 35-42 weeks will be used.

Thus, the following are the estimated rates for four major outcomes examined in this proposal:

I) Death/Grade 3/4 IVH (14 day)	34.2%
II) Death/Grade 3/4 IVH (at d/c, an estimate of 35-42 weeks)	42.9%
III) Death/PVL (at d/c, an estimate of 35-42 weeks)	32.8%
IV) Death/MRI abnormality	58%

Sample size and detectable difference estimates if all centers could participate:
The revised projected sample size required for SUPPORT is 1310 patients (or 328 patients per each of 4 treatment groups). It is clear that not all Network centers have the neuroradiology personnel or technology in place to participate in the entire proposed study. However, according to the NICHD Neonatal Research Network Brain Imaging Survey, 12 of the 14 Networks centers that responded do have conventional brain MRI capability. Thus, a substantial part of the Network could participate in the conventional MRI portion of this proposed protocol. Using an estimate of 80% enrollment in the cranial US/conventional MRI portion of this proposed secondary, 1048 patients would be enrolled. This would provide an estimated 262 patients in each for 4 groups, such that bivariate comparisons will be made between ventilation strategy groups (Early CPAP vs. Control ventilation groups) within each randomized oxygenation strategy, and

between oxygenation strategy groups (Low vs. High SpO2) within each randomized ventilation strategy.

Thus, for the outcome of Death/Grade 3/4 IVH (14 day), using an expected prevalence rate of 34.2% (see above), a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	33.9% = 34.2% to 22.6%
% increase from expected	35.9% = 34.2% to 46.4%

For the outcome of Death/Grade 3/4 IVH (35-42 week), using an expected prevalence rate of 42.9%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	28.4% = 42.9% to 30.7%
% increase from expected	29.4% = 42.9% to 55.4%

For the outcome of Death/PVL by cranial US (35-42 week), using an expected prevalence rate of 32.8%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	34.4% = 32.8% to 21.5%
% increase from expected	36.9% = 32.8% to 44.9%

For the outcome of Death/MRI abnormality (35-42 week), using an expected prevalence rate of 58%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	21.6% = 58% to 45.5%
% increase from expected	20.7% = 58% to 70%

The detectable differences were also calculated for an alpha of 0.01 to adjust for the four primary outcomes. Thus,

For the outcome of Death/Grade 3/4 IVH (14 day), using an expected prevalence rate of 34.2% (see above), a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	40% = 34.2% to 20.5%
% increase from expected	43.2% = 34.2% to 49%

For the outcome of Death/Grade 3/4 IVH (35-42 week), using an expected prevalence rate of 42.9%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	33.6% = 42.9% to 28.5%

% increase from expected 35.2% = 42.9% to 58%

For the outcome of Death/PVL by cranial US (35-42 week), using an expected prevalence rate of 32.8%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected 40.2% = 32.8% to 19.6%
% increase from expected 42.7% = 32.8% to 46.8%

For the outcome of Death/MRI abnormality (35-42 week), using an expected prevalence rate of 58%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected 25.8% = 58% to 43%
% increase from expected 24.8% = 58% to 72.4%

If MRI could not be performed in all sites due to budgetary constraints, clearly differences between groups with respect to the outcome of Death/MRI abnormality would need to be larger in order to detect. If the number of patients involved in the MRI portion of the proposed study were reduced by one-half (to 524), then the sample size per group would drop to 131. In that case:

For the outcome of Death/MRI abnormality (35-42 weeks), using an expected prevalence rate of 58%, a projected sample size of 131 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected 37% = 58% to 36.5%
% increase from expected 35.5% = 58% to 78.6%

However, the estimate of 40% white matter abnormality on MRI among preterm infants at term is conservative, thus the estimate of 58% for the outcome of Death/MRI abnormality may also be low.

Regression Analyses: In addition to bivariate analyses, regression analyses will be undertaken to attempt to adjust for confounding variables in comparisons of treatment groups with respect to neuroimaging findings. The independent association of ventilation strategy will be determined for each neuroimaging outcome (Grade 3/4 IVH at 7-14 days, 35-42 weeks, PVL at 35-42 weeks, MRI abnormality), adjusting for gestational age, weight, and oxygenation strategy. Similarly, the independent association of oxygenation strategy will be determined for each neuroimaging outcome (Grade 3/4 IVH at 7-14 days, 35-42 weeks, PVL at 35-42 weeks, MRI abnormality), adjusting for gestational age, weight, and ventilation strategy.
Neurodevelopmental Outcomes Logistic Regression Models: We propose a novel approach to the comparison of neuroimaging modalities with respect to neurodevelopmental outcomes, that of logistic regression modeling. Numerous neurodevelopmental outcomes studies have used this approach, however previous

studies of brain MRI in the premature infant have lacked the sample size to implement this statistical technique. Models will be developed to include perinatal, demographic, neonatal and socioeconomic factors pertinent to neurodevelopmental outcome as demonstrated in previous reports (14,15) and the univariate and multivariate analyses carried out. Neuroimaging study results (cranial US at 7-14 days, cranial US at 35-42 weeks PMA, and brain MRI at 35-42 weeks) will be added to the model individually and in combination, to determine the adjusted risk for adverse outcome that each imparts, and to ascertain if any two abnormal studies (i.e., early cranial US and MRI, or early and late US) are materially more predictive of neurodevelopmental impairment than any single abnormal study. Ventilatory strategy and oxygen saturation strategy will also be available as crucial neonatal factors that may impact on outcome.

Predictive modeling of outcome: Challenges to the development of a predictive model include the need for both a "model development" data set and a "model validation" data set. Possible solutions to this challenge include splitting the proposed study data set in half, thus creating a development and validation set; or by employing a so-called "boot-strapping" technique by which multiple random samples of the data set are used for calculating confidence intervals for predictions (49). Further analysis will be required to determine the best strategy for predictive modeling in the proposed study.

Further Statistical considerations: Development and comparison of predictive models:

I. Initial model development, the models and their variables.

The sample will be randomly split into a development dataset with 50% of cases and 50% of controls and a test dataset with 50% of cases and 50% of controls. Several models will be developed of which the following are projected to be central models; however, additional models may also be developed:

1. "Classic" risk model, including traditional factors (i.e., gestational age, birth weight, gender, race, maternal education, etc.) as well as "worst" early cranial US
2. Late cranial US model
3. Conventional MRI model

For each model, the number of categorical variables will be restricted to 5 – 10 observations per category cell. When candidate variables exceed this ratio, the best set of significant predictor variables will be chosen by forward selection. In this case, at each step the variable with the most significant effect will be identified and added to the model. The same dataset will be used for the development of each model.

II. Model calibration and goodness-of-fit

Each model will be calibrated using Pearson chi-square, likelihood ratio chi-square, and Hosmer and Lemeshow statistic.

III. Model discrimination and predictive ability

Sensitivity (true positive rate) and specificity (true negative rate) of the models to predict outcome will be evaluated. The receiver-operator curve (ROC) will be used to display model discrimination by plotting sensitivity against specificity. The predictive abilities of

the models will be compared using area under the curve (AUC) analyses (Hanley JA and McNeil BJ, *Radiology* 1982)

IV. Multidimensional model.
Finally, we will attempt to build a model that combines the most significant factors from cranial US and MRI models and compare to the above models.

APPENDICES

Appendix A: Magnetic resonance imaging requirements and image acquisition
Conventional MRI: Network centers that have any "type" of device (i.e., GE, Philips, Siemens, etc.) capable of performing standardized conventional neonatal brain MRI sequences with 4 mm contiguous slices (0mm gap) will be able to participate. All examinations will include conventional fast spin echo (FSE) T1-weighted and T2-weighted sequences as well as fluid attenuated inversion recovery (FLAIR) and gradient echo (GRE) sequences.

Appendix B: Medical instability at 35-42 week PMA MRI
For "medical instability" to be considered the cause of non-acquisition of MRI, one of the following conditions should exist during the entire 35-42 week PMA MRI imaging window:

- The patient is intubated.
- The patient is considered by the attending neonatologist to be critically unstable such that transport to the radiology suite would be unsafe.

Appendix C: Definitions

Early Cranial Ultrasound:

- Grade I: blood/echodensity in the germinal matrix/subependymal area
- Grade II: blood/echodensity in the lateral ventricle without distention
- Grade III: blood/echodensity in the lateral ventricle with distention
- Grade IV: blood/echodensity in the parenchyma
- Cystic areas in the parenchyma: cystic areas in the parenchyma associated with a Grade IV IVH

Late Cranial Ultrasound

- See definitions above
- Cystic periventricular leukomalacia: cystic areas in the parenchyma in the absence of a parenchymal hemorrhage.
- Porencephalic cyst
- Presence of shunt

Conventional MRI interpretation and scoring:

NOTE: Adjustments and amendments to the following scheme may be made after further discussion and input from members of the Steering Committee and SUPPORT Subcommittee.

- C1 = normal

- C2 = minimal subependymal hemorrhage or mineralization with no or mild ventriculomegaly
- C3 = moderate to severe ventriculomegaly
- C4 = parenchymal abnormality
- C5 = periventricular cystic abnormality
- C6 = white matter signal abnormality
- C7 = increased extra-axial fluid
- C8 = cerebellar hemorrhage or mineralization
- C9 = diffuse excessive high intensity signal

Cerebral Palsy ("Neonatal Research Network Follow-Up Study Manual of Operations")
Cerebral palsy at 18-22 months will be diagnosed if definite findings are encountered on exam in any two of the following three areas:

1) Delay in motor milestones – determined using the motor quotient as described in the Manual of Operations.
2) Abnormalities obersed in the classical neuromotor exam, which includes measurement of tone, deep tendon reflexes, coordination and movement (not including eye movement). Any one abnormality, except for isolated low tone or toe walking is sufficient.
3) Aberrations in primitive reflexes and postural reactions – any aberration is sufficient.

Cerebral palsy will be further categorized by type and severity, as described in the Manual of Operations.

Human Subjects

1. Risks to the subjects:

a) Human Subjects Involvement and Characteristics: Infants enrolled in the NICHD Neonatal Research Network SUPPORT trial will be recruited. Inclusion and Exclusion criteria have been defined as stated in the Research Plan. The final population will be dependent upon the number of sites within the Network that participate in this study. Both male and female infants will be enrolled. We expect the study population to be representative of the racial background and gender distribution of the Neonatal Research Network. In 2001, 49% male and 51% female patients constituted the ELBW population of the Neonatal Research Network, of which 43% were black, 38% were white, 15% were hispanic, and 3% were other races.

b) Sources of Materials: Sources of research material will consist of perinatal, demographic and neonatal data collected by research personnel as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality Among VLBW Infants (401-1500 g), and through the data collection mechanisms associated with the SUPPORT trial. Additional data will be obtained through evaluation of brain MRI images by a central reader masked to all patient identifiers and patient outcomes. Data forms will be created, completed by the central MRI reader, and submitted to Research Triangle Institute per protocol. Neurodevelopmental outcome data will be obtained from the NICHD Neonatal Research Network Follow-up Study of ELBW Infants, and per SUPPORT specifications.

c) Potential Risks: The risks and discomforts of participation are minimal as the study relies primarily on data collected for ongoing studies already in progress, and uses non-invasive techniques. Cranial US is performed routinely in all NICU's in the NICHD Neonatal Research Network, is considered standard of care, and techniques would not be altered by this study. Brain MRI at 35-42 weeks postmenstrual age is already routine in several Network centers. Sedation will not be used routinely, although may be used particularly in centers that already do use sedation. Temporary minor skin irritation from tape used to apply MRI-compatible monitoring electrodes may occur, but this risk is unlikely. Temporary transport of a patient to a radiology suite for MRI may also represent a possible risk; however, only those patients considered stable for transport will undergo imaging, and a 7- week window of opportunity for MRI is built into the proposed study. The alternative to obtaining a brain MRI as part of the proposed study is non-enrollment.

2. Adequacy of Protection Against Risks:

a) Recruitment and Informed Consent :

Screening: The individual center will be responsible for devising a screening strategy to identify all potential participants using the study inclusion and exclusion criteria. Screening, identification and informed consent procedures should be completed by 14 days of age as "early cranial US" must be performed by this time.

Informed consent: Each participating center will follow procedures for developing informed consents as set out by their Institutional Review Board (IRB). The parents of all infants enrolled in SUPPORT will be approached to participate in this secondary study, and informed consent must be obtained by the individual center. Informed consent will be obtained by the Principal Investigator or his/her designee.

Eligible infants not enrolled: The reasons for non-enrollment of eligible infants will be documented. Short- and long-term outcomes of eligible infants not enrolled in this study will be documented as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality in Very Low Birth Weight (VLBW) Infants (Generic Data Base (GDB)) and, if enrolled, as part of the ongoing NICHD Neonatal Research Network ELBW Neurodevelopmental Follow-Up Study.

No MRI obtained for enrolled infants: The objective of the proposed study requires acquisition of cranial US and MRI at 35-42 weeks PMA; if the patient is deemed medically unstable during the entire 35-42 week PMA period, an MRI will not be obtained. Other reasons for inability to obtain the MRI will also be documented.

b) Protection against risk: Every effort will be made to protect study patients from potential risks of participation. Stability of study patients for transport to a radiology suite for brain MRI will be assessed by the attending neonatologist at each participating site. Should a patient be judged to be unstable for transport to the radiology suite, a 7-week window of opportunity for MRI (35-42 weeks postmenstrual age) has been provided in the protocol. Any adverse events with regard to obtaining neuroimaging studies among enrolled patients will be documented and submitted to NICHD, the data center, and the local IRB. The NICHD Neonatal Research Network has an independent Data Safety Monitoring Committee (DSMC), which would provide continuous oversight of patient safety and risk factors for the duration of the study. The DSMC will review the study on at least an annual basis.

3. Potential Benefits of the proposed research to the subjects and others: The potential benefits of participation to an individual patient include identification of structural anomalies by MRI that would not have been identifiable by ultrasound. This may allow for early, targeted intervention for the individual patient that otherwise would not have been undertaken. Other potential benefits would be to future extremely preterm patients after results of this prospective study are known (see below).

4. Importance of the knowledge to be gained:
Provide a thorough neuroimaging monitoring arm for SUPPORT: Although cranial US is a standard diagnostic procedure in the NRN, the proposed study would provide a framework for specifically timed cranial US studies, which would be more appropriately comparable. In addition, subtle but arguably extremely important findings consistent with brain injury would be detectable by MRI.
Counseling, follow-up: Detection of an injury pattern which is consistent with later neurodevelopmental delay will be useful for counseling and targeted, early follow-up. Identifying such a tool would provide a link to later research in early intervention.
Clarify the pathogenesis of injury leading to neurodevelopmental impairment: Further delineation of pathophysiologic correlates of later outcome could possibly be linked with perinatal and neonatal factors, which would 1) focus future research and intervention on clinical events associated with the pathophysiologic hallmark, 2) provide important data leading to further study of the pathogenesis and timing of injury, and 3) assess neuroanatomic localization of subtle injury associated with later neuromotor abnormalities.
Contribution to the literature with respect to diagnostic strategies for the extremely preterm population: Previous neuroimaging practice parameters have concluded that insufficient evidence exists to recommend advanced neuroimaging for premature infants for prediction of neurodevelopmental outcomes. The proposed study would address this significant gap in the collective literature.

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From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT secondary?
Date: Monday, October 18, 2004 11:11:35 AM

Rose -

Mondays, Tuesdays and Wednesdays are terrible for me - I am in class all day except for a few brief periods. I could call you - it would be around 2 pm-2:30 pm EST? Is that OK?

Susan

>Susan
>I will call you later this AM to discuss the proposal. I believe a
>point-by-point response is warranted.
>
>talk to you soon
>Rose
>
>-----Original Message-----
>From: Susan Hintz [mailto:srhintz@stanford.edu]
>Sent: Saturday, October 16, 2004 11:14 AM
>To: Higgins, Rosemary (NIH/NICHD)
>Subject: SUPPORT secondary?
>
>
>Hi Rose,
>
>I'm wondering if you've had a chance to mull over the
>questions/comments in the email I sent you and Neil after the Network
>meeting about the SUPPORT secondary? I have not heard from Neil. I
>am just getting increasingly tense, mostly because my schedule is
>COMPLETELY packed, and I want to be VERY directed about any revisions
>to the protocol.
>
>The reviewing body for head imaging/SUPPORT protocol may not
>understand that DTI is an incredibly expensive proposition. Although
>it would be nice to have a huge study focused on DTI, it's NOT going
>to happen at this moment. Maybe in the future. I think it's better to
>be realistic - the SUPPORT trial could be used to look PRIMARILY at
>early and late HUS both as a safety check for SUPPORT, and at early
>vs. late US in models for neurodevelopmental outcome. As I have
>mentioned before, I think SUPPORT should require in the protocol both
>a 7-14 day HUS and SOME head imaging at near 36 weeks. If the
>network center does MRI now, fine - the cheapest solution to having
>EVERYBODY have a HUS would be to pay for the HUS at 36 weeks in the
>centers doing the MRI at 36 weeks. At least then we would have some
>paired MRI and HUS at 36 weeks.
>
>OK - enough of that topic.
>
>Just to update you, ADC notified me that the revised article is now
>DEFINITELY accepted for publication. As you know, I have already
>sent out the <25 week neurodevelopmental outcomes paper to Pediatrics

>(probably won't hear anything until at least Thanksgiving). I have
>also been working with RTI on the data analysis for the projects for
>SPR. Krisa gets off service next week, and she and I will have to
>discuss the HUS and PiNO issues.
>
(b) (6) [redacted]
>
>Thanks again for your support -
>
>Susan
>--
>Susan R. Hintz, M.D.
>Assistant Professor of Pediatrics
>Division of Neonatal and Developmental Medicine
>Stanford University School of Medicine
>750 Welch Road, Suite #315
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From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT protocol
Date: Monday, October 11, 2004 1:31:34 PM

Rose
yes
Seetha

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 06, 2004 7:52 AM
To: Abbot Laptook (E-mail); Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (E-mail)
Cc: 'petrie@rti.org'; 'bkh@rti.org'
Subject: SUPPORT protocol

Neil Finer has a number of requests for the SUPPORT protocol from other investigators - primarily those involved with POST ROP, BOOST II. He would like to provide it to them. Neil wants to keep them involved and informed as we are going to use the same oximetry intervention, developed by us, and we will be able to perform a prospective meta analysis using all the studies if we adhere to this. This would be very powerful and could represent 5000 infants. The major collaborators are William Tarnow-Mordi, Cynthia Cole and Lisa Askie.
Please send me a YES/NO vote by October 12, 2004 to provide the protocol (once finalized) to these investigators.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine NICHD, NIH
6100 Executive Blvd., Room 4B03B
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(for Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

From: David Stevenson
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT protocol
Date: Wednesday, October 06, 2004 11:06:39 AM

Rose,
My vote is yes.
David

At 04:52 AM 10/6/2004, you wrote:

> Neil Finer has a number of requests for the SUPPORT protocol from other investigators - primarily those involved with POST ROP, BOOST II. He would like to provide it to them. Neil wants to keep them involved and informed as we are going to use the same oximetry intervention, developed by us, and we will be able to perform a prospective meta analysis using all the studies if we adhere to this. This would be very powerful and could represent 5000 infants. The major collaborators are William Tarnow-Mordi, Cynthia Cole and Lisa Askie.
> Please send me a YES/NO vote by October 12, 2004 to provide the protocol (once finalized) to these investigators.
> Thanks
> Rose
>
> Rosemary D. Higgins, M.D.
> Program Scientist for the Neonatal Research Network
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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Neil Finer
Subject: RE: SUPPORT protocol
Date: Wednesday, October 06, 2004 8:02:01 AM

Rose: Yes, I agree. wally

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 06, 2004 6:52 AM
To: Abbot Laptook (E-mail); Wally Carlo, M.D.; Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (E-mail)
Cc: 'petrie@rti.org'; 'bkh@rti.org'
Subject: SUPPORT protocol

Neil Finer has a number of requests for the SUPPORT protocol from other investigators - primarily those involved with POST ROP, BOOST II. He would like to provide it to them. Neil wants to keep them involved and informed as we are going to use the same oximetry intervention, developed by us, and we will be able to perform a prospective meta analysis using all the studies if we adhere to this. This would be very powerful and could represent 5000 infants. The major collaborators are William Tarnow-Mordi, Cynthia Cole and Lisa Askie.
Please send me a YES/NO vote by October 12, 2004 to provide the protocol (once finalized) to these investigators.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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From: Susan Hintz
To: neil finer
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT secondary
Date: Wednesday, September 29, 2004 8:31:42 PM
Attachments: SUPPORT_neuroimaging.rev.doc
Hintz MRI prtcl summary review 19Aug04.doc
DRAFTBudgetrevised.doc

Hi Neil and Rosemary,

Since you have both been at the steering committee meeting, now is probably a good time to find out how things are going. I'm sure you both have seen the Protocol Committee responses to my last revision of the SUPPORT secondary. I appreciate their responses, but I think they are not completely in harmony with the comments from the individuals associated directly with the SUPPORT trial, or with our own conversations. Specifically, comments from the Protocol Committee suggested that the hypotheses focus (again) on neurodevelopmental outcome and neuroimaging - we had clearly discussed the need for a "safety arm" of the SUPPORT trial, and revisions in that direction were made with those needs in mind. In addition, monetary concerns are very important - although the Protocol Committee comments suggested that DTI be returned to the secondary as a focus, I would submit that DTI is unlikely to be performed (if we are lucky) at any more than 2 or 3 centers, and the cost of adding additional centers would be prohibitive and technically not feasible. As you both know, an ancillary is planned for the DTI portion that centers could take part in if they wished.

I am attaching both the June-July version of the SUPPORT secondary, the June-July version of the budget, as well as the Protocol committee comments. I would appreciate your direction in any needed revisions. Some of my other comments and questions I included in my July 26th email. Also note that the latest update on the MRI-US survey from Betty Hastings still had site responses missing. I will ask her to re-send to those sites.

Thanks for your help,

Susan
--
Susan R. Hintz, M.D.
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Susan Hintz, Stanford University

NEUROIMAGING AND NEURODEVELOPMENTAL OUTCOME: A SECONDARY TO SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL (SUPPORT)

A. Abstract/Statement of Problem

Cranial ultrasound (US) is currently used for brain imaging in the extremely preterm population, but this modality cannot detect subtle brain injury that may be responsible for later neuromotor and cognitive delay. Magnetic resonance imaging (MRI) can identify brain structural abnormalities and white matter injury better than cranial US. The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) will evaluate if permissive ventilation strategies and lower SpO_2 targets will result in increased rates of survival without bronchopulmonary dysplasia (BPD) and survival without retinopathy of prematurity (ROP) among 24-27+6/7 week EGA infants. It is not known whether differing ventilation and oxygenation management approaches could lead to adverse consequences with respect to brain injury. We propose a secondary study of specifically timed cranial US and brain MRI to test the hypothesis that these ventilation and oxygenation strategies will not be associated with an increase in death or brain injury (Grade 3/4 IVH by cranial US at 7-14 days or 35-42 weeks, abnormal brain MRI at 35-42 weeks). Extremely premature infants are also at very high risk for neuromotor and neurodevelopmental impairment, with reported rates of cerebral palsy (CP) ranging from 11-20%, and of severe cognitive delay ranging from 30-60%. The power of MRI to predict neurodevelopmental outcome better than early and/or late cranial US among preterm infants is not yet known, but preliminary studies are promising. We therefore propose to use neurodevelopmental follow-up data at 18-22 months corrected age, already part of SUPPORT, to assess comparative and combined predictive capabilities of these neurodiagnostic modalities ("early" cranial US, "late" cranial US and MRI). The NICHD Neonatal Research Network is uniquely positioned to embark upon such a project, which would be the first multicenter, prospective study to investigate these important questions.

B. Objective

We propose a secondary, prospective study of cranial US at 7-14 days ("early") and 35-42 weeks postmenstrual age (PMA) ("late"), and brain MRI at 35-42 weeks PMA among infants enrolled in SUPPORT to determine if the ventilatory or oxygen saturation interventions are associated with differences in the outcomes of death or abnormal neuroimaging findings (death/grade 3/4 IVH on "early" US, death/grade 3/4 IVH on "late" US, death/PVL, death/abnormal MRI). We also propose to evaluate and compare the capabilities of MRI and early and late cranial ultrasound (US) to predict neuromotor and neurodevelopmental outcome at 18-22 months corrected age through development of predictive models.

C. Hypotheses

Primary Hypotheses

1) There will be no differences in frequency of Death/Grade 3/4 IVH on early or late US between Low and High SpO_2 groups, or between Early CPAP and Control ventilation groups

2) There will be no difference in frequency of Death/PVL between Low and High SpO2 groups, or between Early CPAP and Control ventilation groups
3) The frequency of Death/abnormal findings on conventional brain MRI at 35-42 weeks postmenstrual age (PMA) will not be different between Low and High SpO2 groups, or between Early CPAP and Control ventilation groups.

Secondary Hypotheses
1) Multivariate predictive modeling will show that abnormal findings on conventional brain MRI at 35-42 weeks postmenstrual age (PMA) will be more strongly associated with cerebral palsy and neurodevelopmental impairment than abnormal findings on cranial US at 18-22 months corrected age.

D. Specific Aims

1) To obtain consistently performed, timed and interpreted neuroimaging studies in extremely preterm infants enrolled in SUPPORT:
    a. cranial US at 7-14 days of age
    b. cranial US at 35-42 weeks PMA
    c. MRI at 35-42 weeks PMA
2) To compare early and late US, and MRI findings between Low and High SpO_2 groups, and between Early CPAP and Control ventilation groups.
3) To utilize the NICHD Neonatal Research Network longitudinal follow-up programs to assess neurodevelopmental outcomes at 18-22 months corrected age, as described in SUPPORT.
4) To examine the independent associations of neuroimaging findings with neurodevelopmental outcomes through logistic regression modeling.
    a. Regression models would include traditional risk factors as covariates, with stepwise addition of the various neuroimaging modalities and findings, alone and in combination.
5) To develop models to estimate the prognostic utility of specific neuroimaging modalities and findings, alone and in combination, for neurodevelopmental outcomes.

E. Background, Significance and Rationale

The importance of an advanced neuroimaging component to SUPPORT:

SUPPORT will be the largest randomized controlled trial of ventilatory and oxygen saturation target management in extremely premature infants to date. Although the primary outcomes for the SUPPORT focus on survival without BPD and survival without ROP, it will be crucial to evaluate the potential impact of study interventions on both neuroimaging findings and neurodevelopmental outcomes. One possible concern could be that lower oxygenation parameters and less aggressive ventilatory management may be associated with a higher incidence of brain injury. This position might be extrapolated from early observations in preterm infants suggesting that intubation and mechanical ventilation decrease arterial blood pressure fluctuation and intraventricular hemorrhage (1), from reports correlating low estimated neonatal cerebral oxygen delivery with subsequent brain injury (2), or from studies of near-term and term hypoxic brain injury.

However, other investigations suggest that the opposite may be true; more aggressive ventilation strategies leading to hypocapnia may place the premature infant at higher risk for reduced cerebral blood flow (CBF) and subsequent white matter injury. This CBF-carbon dioxide reactivity observed in adult animals may be blunted or incomplete in newborn and preterm animals (3,4). Nevertheless, several clinical case series of preterm infants have demonstrated strong associations of hypocapnia with significant abnormal findings on brain imaging and with adverse neurodevelopmental outcome (5-8), although other important risk factors were also identified.

At the very least, neuroimaging abnormalities in preterm infants are likely to be the result of a multifactorial process. Emerging evidence points to the unique vulnerability of the preterm infant brain in several respects. Low blood flow to the cerebral white matter and impaired cerebrovascular autoregulation in premature infants (9-11) may make subtle brain ischemic injury more likely. Coupled with this tendency to ischemic injury, is the vulnerability of developing oligodendroglial cells to damage (see below). Finally, it is possible that effects of exposure to *in utero* infection, frequently suspected in extremely preterm infants, may potentiate brain cellular injury caused by mild to moderate ischemia (12,13).

Summary: Given the interventions to be undertaken in SUPPORT, and the complexity and multifactorial nature of the development of white matter injury in the premature brain, advanced neuroimaging could be a critical safety component to the trial. This proposed secondary to SUPPORT would provide important additional information to investigators with respect to the impact of respiratory management on subtle brain injury.

The need to investigate emerging brain imaging modalities:

Premature infants are at high risk for neuromotor and neurodevelopmental impairment. Recent reported rates of cerebral palsy (CP) at 18-24 months corrected age range from 11-20%, and of cognitive delay range from 30-60% for the extremely low birth weight (ELBW) population (14-16). Yet, despite numerous investigations, the causes for these impairments remain unclear. Correlation of specific neonatal factors, particularly neuroimaging findings, with adverse neuromotor and neurodevelopmental outcomes are frequently, but not consistently demonstrated. Many studies have emphasized the association of cranial US abnormalities including intraventricular hemorrhage (IVH) grades 3 and 4, periventricular leukomalacia (PVL) and ventricular dilatation with subsequent neurologic and cognitive impairment (14-20). Most investigators have found abnormalities on cranial US to be an independent risk factor for neuromotor abnormalities, but not necessarily for cognitive impairment.

But, the finding of severe cranial US abnormalities is not uniformly predictive of adverse neuromotor outcome in the premature population. In a study of perinatal correlates of neurologic impairment at 18-22 months corrected age among VLBW infants (20), only 52% of the infants with CP on follow-up had had severe cranial US abnormalities. This finding was in contrast to a 12% rate of severe cranial US abnormalities among matched controls without CP. In a neurodevelopmental follow-up study of ELBW infants in a multicenter, double masked, randomized controlled trial of indomethacin prophylaxis in preterms (TIPP), rates of survival without neurosensory impairment were found to be similar between treatment groups although incidence of

grade 3 or 4 IVH on cranial US had been significantly reduced by treatment with indomethacin (21).

Smaller studies have investigated the capabilities of cranial US at term to predict CP among preterm infants, revealing that the sensitivity of this diagnostic tool is only approximately 60% (22,23). Other reports have indicated that cystic PVL may be detected in infants without previous cranial US abnormalities at several months of age (24-26). These studies suggest that only certain types of brain injury may be detectable with cranial US, and that timing of studies may be crucial. Furthermore, the radiologic changes associated with PVL may be visible by US only at a particular point in time; if cysts do not form as a result of injury leading to PVL, it may not be visible by US. Thus, injury could have occurred but would not be detected by US.

Summary: Cranial US, the imaging modality currently considered to be standard of care, may not be sensitive enough to detect brain injury that is responsible for later neuromotor or neurodevelopmental delay among ELBW infants.

MRI compared with cranial US to assess of brain injury and predict neurologic outcome

MRI provides a more complete and anatomically detailed evaluation of the neonatal brain. Several studies have compared the relative capabilities of US and MRI to detect brain injury among preterm infants in the newborn period. These reports concluded that MRI detects white matter injury better than HUS (27-29), and provides additional information regarding hemorrhage and cystic changes not noted by cranial US. Childs, et. al. assessed MRI and serial cranial US in both preterm and term infants, and concluded that MRI was more sensitive in identifying periventricular white matter lesions (30). However, neurodevelopmental outcome of the infants in those studies were not reported.

Few studies have compared MRI with cranial US in terms of their capabilities to predict neurodevelopmental outcome among premature infants; those are small, primarily single-center efforts. Furthermore, due to variability of timing, of imaging, and differences in MRI scoring and interpretation, the studies are difficult to compare. Valkama, et. al. (31) assessed MRI compared with cranial US performed at term in 51 VLBW, preterm infants (<34 weeks). Twelve infants were diagnosed with CP at 18 months corrected age. MRI parenchymal lesions predicted CP with 100% sensitivity and 79% specificity whereas US at term predicted CP with 67% sensitivity and 85% specificity. The authors concluded that MRI was the more reliable methodology. Stanford University researchers (see below "Preliminary Studies and Results") have completed a prospective study of neuroimaging among VLBW, preterm infants with neurodevelopmental follow-up at 18-22 months and 30 months corrected age (32). The group demonstrated that MRI at term predicted CP with superior sensitivity and positive predictive value to early cranial US.

Other studies have suggested the potential prognostic advantages of MRI compared with cranial US. Roelant-van Rijn and colleagues (33) studied 61 preterm infants with cranial US, and MRI within the first weeks of age and/or at term. MRI at term was found to be helpful in delineating internal capsule abnormalities, which was considered to be useful in predicting later hemiplegia. Other preliminary reports include that of Austin, et. al. (34) in which 93 VLBW infants evaluated with brain MRI at term underwent

neurodevelopmental assessments at one year corrected age. White matter injury on MRI at term was correlated with neuromotor abnormalities such as hypertonicity, hypotonicity, and motor delay. In a very small group of premature infants <36 weeks, Miller, et. al. (35) showed that cerebellar hemorrhages detected by MRI, even if not associated with white matter injury, appeared to be associated with adverse neurodevelopmental outcome at 12 months.

There are potential criticisms to these studies. In most cases, MRI was compared with only "late" cranial US or only "early" US; a more complete comparison would include both early and late cranial US, demonstrating that the design of neuroimaging collection strategies in prospective studies is crucial. Many studies focus narrowly on neuromotor outcome, specifically incidence of CP as outcome variables. A broader neurodevelopmental assessment and comparison is warranted. Finally, all studies of MRI findings and correlation with neurodevelopmental outcomes in preterm infants thus far are small; it is therefore not possible to draw powerful conclusions, especially with regard to ELBW patients. In fact, the recently published "Practice Parameter: Neuroimaging of the Neonate" (36) failed to definitively recommend routine MRI for VLBW preterm infants in part due to the lack of follow-up studies. But, many of the reports reviewed above were not available during the development of the "Practice Parameter".

Summary: Studies to date suggest that MRI may be a more powerful tool in predicting adverse neuromotor outcome among preterm infants. However, timing of studies vary between published reports, and very few prospective neurodevelopmental follow-up investigations have been undertaken to assess the comparative prognostic capabilities of these neuroimaging techniques for neuromotor and cognitive outcomes.

The importance of subtle white matter injury

Periventricular leukomalacia (PVL) has been categorized as "focal" and "diffuse" (37,38). Focal PVL has been described as the result of severe ischemic-necrotic injury and is located deep in the white matter. This type of injury may lead to the development of cystic changes or significant findings that can be detected by cranial US or conventional MRI. Diffuse PVL is the result of less severe injury, diffusely located in the white matter. The mechanism for diffuse PVL may be multifactorial, including: 1) mild to moderate ischemia due to decreases in cerebral blood flow consistent with impaired autoregulation, 2) vulnerability of immature oligodendroglial cells to ischemic injury and damage by chemical mediators, and 3) oligodendroglial cell susceptibility to injury and death after intraventricular hemorrhage due to creation of oxygen free radicals. The sensitivity of the immature oligodendroglial cells to cytokine-induced injury may help to provide a pathophysiologic explanation to the observations of increased CP rates among infants born to mothers with chorioamnionitis, and among infants with early sepsis.

Diffuse PVL may be a clinically important and prevalent white matter injury in the preterm infant. Yet, diffuse PVL is unlikely to be seen by cranial US. Diffuse PVL may also be challenging to detect reliably on conventional MRI. However, in a study by Counsell et. al. (39), diffuse excessive high signal intensity (DEHSI) in the white matter of preterm infants at near-term was associated with higher apparent diffusion coefficient

values on diffusion weighted MRI. This finding suggested that subtle injury, causing changes in cellular differentiation and probable preferential death of preoligodendrocytes, resulting in diffuse PVL (40), may be structurally visible in the form of DEHSI. The developmental significance for the preterm infant is not known. It is also important to note that all subtle white matter injury is unlikely to be detectable even by MRI.

Summary: IVH and focal cystic PVL are detectable by conventional MRI or even cranial US. However, more subtle factors and injuries may lead to oligodendroglial cell death and diffuse PVL. Diffuse PVL is not likely to be detected by cranial US, but might be detected by MRI. Such injury may have a substantial impact on normal white matter development and neuromotor outcome in the preterm infant; however, this question has been poorly studied in a large-scale, prospective manner.

Preliminary Studies and Results

A coordinated effort among neonatologists, radiologists, engineers, technicians and developmentalists has been in place at Lucile Salter Packard Children's Hospital and the Lucas Center for Nuclear Magnetic Resonance at Stanford University since the late 1990's. The objective of this group has been to combine the talents and expertise from various fields of science to investigate novel, potentially clinically relevant neuroimaging approaches in term and preterm infants. As a result, a strong infrastructure exists to allow for the development and implementation of further prospective studies and trials of MRI and DTI in the neonatal population.

Cranial US vs. conventional MRI for prediction of CP in VLBW infants: Infants of <1250 grams and <30 weeks EGA were enrolled a prospective observational study of the capabilities of early cranial US compared with conventional MRI at near-term to predict CP at 18-22 months corrected age, and 30 months (32). Cranial US was obtained twice during the first two weeks of life, and the most abnormal findings were used for analysis. Conventional MRI and cranial US were scored with respect to size of hemorrhage, parenchymal involvement, and ventricular dilitation. 62 infants participated in the study, with one excluded from analysis due to a later diagnosis of muscular dystrophy. The sensitivity and specificity of near-term MRI for predicting CP at 18-22 months were 71% and 91% respectively. The sensitivity of MRI for predicting CP at 30 months of age increased to 86% with the specificity remaining high at 89%. Although the specificity was comparable to MRI, the sensitivity of US to predict CP was only 29% at 18-22 months and 43% at 30 months. The positive predictive value of US was 22% at 18-22 months and 33% at 30 months.

This study, one of the largest prospective comparative neuroimaging studies of VLBW infants and neurodevelopmental outcome, supports the suggestion that conventional MRI may be superior to cranial US with respect to prediction of neuromotor abnormalities. There are limitations to this study, however. Comparison cranial US were performed early in the hospital course (<2 weeks), and no US contemporaneous with the MRI were routinely obtained. Recent studies by other investigators have also determined that, among VLBW infants, early cranial US poorly predicts non-cystic white matter injury on MRI at term (41). Also, previous reports by

Valkama, et. al. (31) suggest that cranial US at term was a substantially less sensitive predictor of CP than MRI at term. Nevertheless, a thorough comparison would include early and later cranial US determinations to evaluate the potential combined prognostic power of early and late cranial US compared with MRI at term. In addition, this study was significantly limited by small sample size, with only seven infants diagnosed with CP on neurodevelopmental follow-up. Sample size considerations also restricted possibilities for multivariate modeling of outcomes, and meaningful analysis of Bayley Scales of Infant Development II scores. All of these limitations could be addressed in the proposed prospective multicenter study.

F. Research Design and Methods

1. Study Design: This proposed secondary to SUPPORT is a prospective study of traditional (cranial US at 7-14 days and 35-42 weeks PMA) and advanced (MRI at 35-42 weeks PMA) neuroimaging with respect to SUPPORT randomized ventilation and oxygen saturation interventions. The capabilities of these neuroimaging modalities to predict neurodevelopmental outcome at 18-22 months corrected age will also be assessed.

Perinatal, demographic and neonatal data will be collected as part of the ongoing NICHD Neonatal Research Network Survey of Morbidity and Mortality Among VLBW Infants (401-1500g) for the purposes of the study. Cranial US will be obtained at 7-14 days and at 35-42 weeks PMA. *Clinical* interpretation of cranial US will continue to be performed at individual Network sites, but for purposes of research outcomes, cranial US should ideally be interpreted by central readers. Brain MRI will be obtained at 35-42 weeks PMA; MRI will be interpreted by a central reader(s) for purposes of research outcomes, but clinical interpretation will be performed at individual Network sites. Detailed neuromotor and neurodevelopmental examinations will be undertaken at 18-22 months corrected age as part of the NICHD Cooperative Multicenter Network of Neonatal Intensive Care Units: Follow-Up of ELBW Infants (401-1000g), and per SUPPORT protocol.

Statistical analysis will include bivariate analyses, and logistic regression modeling to 1) assess the association of SUPPORT ventilation and oxygenation randomized treatment groups with neuroimaging, 2) evaluate the strength of independent associations of specific neuroimaging findings with neurodevelopmental outcomes and 3) develop predictive models.

2. Study Population

Inclusion Criteria

- Enrolled in the NICHD Neonatal Research Network SUPPORT study
- Cranial ultrasound can be obtained at 7-14 days of age and at 35-42 weeks PMA
- Brain MRI can be obtained per study specifications (see Appendix D) at 35-42 weeks PMA

Exclusion Criteria

- Patient likely to be discharged or transferred from the Network center with MRI capability by 35-42 weeks PMA.
- Patient unlikely or family unwilling to participate in neurodevelopmental assessment at 18-22 month corrected age

- Presence of known or suspected congenital anomalies including:
  - ➤ Chromosomal anomalies
  - ➤ Complex congenital heart disease (PDA, small muscular VSD or PFO are NOT considered to be congenital heart disease for the purposes of this study)
  - ➤ Congenital infection (TORCH, untreated maternal HIV, syphilis)
- Prior enrollment in conflicting clinical trial
- Lack of informed consent

Enrollment of Subjects

Screening: Each center will be responsible for devising a screening strategy to identify all potential participants using the study inclusion and exclusion criteria. Screening and identification of patients should take place by 14 days of age since the "early cranial US" must be performed at 7-14 days.

Informed consent: Each participating center will follow procedures for developing informed consents as set out by the local Institutional Review Board (IRB). It is expected that the parents of all eligible infants will be approached to participate in this prospective study, and informed consent must be obtained by the individual center.

Eligible infants not enrolled: The reasons for non-enrollment of eligible infants will be documented. Short- and long-term outcomes of eligible infants not enrolled in this study will be documented as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality in VLBW Infants (Generic Data Base (GDB)) and, if enrolled, as part of the ongoing NICHD Neonatal Research Network ELBW neurodevelopmental follow-up study.

No MRI obtained for enrolled infants: An important objective of the proposed study requires acquisition of MRI at 35-42 weeks PMA; it is important that each participating center make this a priority. However, it is understood that if the patient is deemed medically unstable (Appendix B) during the entire 35-42 week PMA period, an MRI will not be obtained. Other reasons for inability to obtain the MRI will also be documented.

3. BASELINE DATA, NEUROIMAGING, NEURODEVELOPMENTAL FOLLOW-UP

a. Baseline Data: Perinatal, demographic and in-hospital variables

i. INTRODUCTION AND FEASIBILITY: This secondary protocol will not require substantial data collection in addition to that already in place at participating centers; nor will it mandate patient management. The data collection instruments will be those already in routine use in the participating centers through the NICHD Neonatal Research Network Survey of Morbidity and Mortality in VLBW Infants. These data are obtained through the use of "Generic Data Base forms" which allows for consistent accrual of demographic, perinatal and neonatal variables among this high-risk population.

ii. METHODS: Research nurses at participating centers will collect data using the standardized Generic Data Base Forms NG02, NG03, NG05 and NG07, and the definitions detailed in the Manual of Operations. Perinatal, demographic and in-hospital data collected will be from those data collection instruments. Additional queries will attempt to delineate the potential independent contribution of hypotension and hypocarbia, purported to be causes of cerebral hypoperfusion (42-46) leading to diffuse

or focal neonatal brain injury, to abnormalities on MRI and DTI. These questions will be coordinated with the SUPPORT protocol subcommittee and focus on 1) need for pressors and 2) the degree of hypocarbia experienced

Since these infants will be participating in the SUPPORT trial, information regarding ventilation strategy and oxygen saturation randomization arms will also be included in neurodevelopmental outcomes models as additional factors.

b) Neuroimaging studies

i. INTRODUCTION AND FEASIBILITY: Changes in the approach to neuroimaging may be required for implementation of this research protocol at participating centers; the extent of the changes will depend upon the procedures already in place at each individual center. Within the Neonatal Research Network, cranial US should already routinely be performed in ELBW infants 7-14 days of age window, and are frequently performed at near-term. For the purposes of this study however, central neuroimaging readers should ideally be secured for both early and late cranial US since disparate interpretations of would potentially complicate analysis.

A brain MRI at near-term is part of the routine VLBW infant care protocol in some of the Network centers. A survey will be sent to Network PI's respect to extent of this practice is pending. However, because this diagnostic approach is emerging, and due to the current lack of standardized grading systems, MRIs must be interpreted by central pediatric neuroradiologist readers.

Network centers with devices capable of performing neonatal conventional brain MRI (4 mm slice, 0 gap) could participate in the MRI portion of this proposed study. Due to budgetary considerations, it is possible that implementation of this proposed secondary may be limited only to selected Network sites. The most conservative approach would be that only those sites in which MRI is currently, or will soon be, implementing routine near-term MRI will participate in this proposed secondary.

ii. METHODS:

1) "Early cranial ultrasound": A cranial ultrasound will be obtained at 7-14 days of age. Results will be interpreted as indicated in the Manual of Operations (See Appendix C), and reported in the NG03 form, but central readers would ideally formally interpret ultrasounds.

Although not currently *required* within the parameters of the NICHD Neonatal Network VLBW Registry, recent ELBW neurodevelopmental follow-up studies from the NICHD Neonatal Research Network reveal that virtually all of these extremely high risk infants surviving to the 18-22 month visit have had at least one cranial US early in the course of their hospitalization. Furthermore, the "Practice Parameter" for neuroimaging in the neonate recommends *screening cranial US should be performed on all infants with EGA of <30 weeks at 7-14 days of age* (36); it is likely that Network centers have already implemented this practice to patient care protocols.

2) "Late cranial ultrasound": A cranial ultrasound will be obtained at 35-42 weeks PMA, and within 7 days of brain MRI. All late cranial US will be reported in the NG03 form as indicated in the Manual of Operations (See Appendix C), and will ideally be interpreted by central readers.

Late cranial US is not currently required in the Network paradigm; however, the importance of this later exam to the completeness of the proposed study is clear. Also, the "Practice Parameter" as referred to above (36) recommends that *cranial US should be optimally repeated at 36-40 weeks' postmenstrual age*, so it is likely that many

3) Brain MRI: A brain MRI will be obtained at 35-42 weeks PMA, and within 7 days of the "late cranial ultrasound". Images will be acquired as described in Appendix A. Conventional MRI images will be transferred to Stanford University for interpretation and scoring by central pediatric neuroradiologist reader(s) (Patrick Barnes, M.D., and others as suggested by the Steering Committee) who will be masked to any unique patient identifiers and to patient history and outcome. Dr. Barnes is a highly regarded, widely published pediatric neuroradiologist with extensive experience in the field of MRI, MR spectroscopy, diffusion weighted and diffusion tensor imaging. In addition to his dedicated work at Stanford University, Dr. Barnes has also collaborated with researchers such as TE Inder, PS Huppi and JJ Volpe. Dr. Barnes is an expert in the timing of fetal and neonatal brain injury using methods such as MRI and MRS.

MRI interpretation and data access: Conventional MRI images will be interpreted and scored by a central neuroradiology reader (Appendix C). The central reader(s) will be responsible for completion of data forms and data transfer to the Network Data Center. Each participating center is expected to counsel families with regard to MRI findings on the basis of its own neuroradiologist's interpretation of the images.

Sedation issues: MRI studies are performed without sedation at Stanford University. Patients are imaged following a feeding, ear plugs (MiniMuffs, Natus) are used to reduce the noise by up to 50% and patients are bundled to preserve warmth, maintain sleep and reduce patient motion. Of the 14 sites that responded to an earlier NICHD Neonatal Research Network Brain Imaging Survey, five indicated that they already use sedation for MRI. Another six sites indicated that sedation is used if clinically necessary. One site responded that sedation is not used. Responses from two centers were not clear. At Stanford, the approach of "feeding and swaddling" has yielded successful conventional MRI imaging with excellent quality in almost all cases. Obtaining "excellent" quality DTI sequence data is certainly more challenging. Sedation, if needed, would clearly increase the likelihood of obtaining a high quality scan. Network centers in which sedation is standard of care, and MRI is routinely performed, should certainly be able to continue their current approach. Although several of the sites have already indicated that sedation is used routinely, it is appreciated that the use of sedation in the context of a research protocol may make IRB approval more difficult. One possible solution for centers with such challenges would be to present two consent forms: the first for participation in the study itself, indicating that "feeding and swaddling" methods would be tried; the second, for consent to use sedation if this conservative approach were not successful, or if it is considered medically inadvisable to implement the "feeding and swaddling" approach (i.e., severe reflux).

c) Neurodevelopmental Follow-up

i. INTRODUCTION AND FEASIBILITY: Neurodevelopmental follow-up for ELBW infants is already a focused objective within the NICHD Neonatal Research Network; all Network centers have complete neurodevelopmental assessment teams and patient

tracking infrastructure in place. In addition, neurodevelopmental follow-up is already a part of SUPPORT protocol.
ii. METHODS: Follow-up visit will be conducted at 18-22 months corrected age as described in the "NICHD Neonatal Research Network ELBW Follow-Up Study Manual of Operations" (see Appendix C). An exam for neurological exam for cerebral palsy will be performed. The Bayley Scales of Infant Development (Bayley N. Bayley Scales of Infant Development-II. San Antonio, TX: Psychological Corporation; 1993) will be administered by a Bayley Examiner certified for the Follow-Up Study. In addition to neurodevelopmental assessments, information regarding socioeconomic status, level of education of the primary caregiver, and marital status is routinely obtained at the 18-22 month visit.

4. STATISTICAL CONSIDERATIONS

Outcomes:
Primary outcomes considered will include

- Death/Grade 3/4 IVH on 7-14 day cranial US
- Death/Grade 3/4 IVH on 35-42 week cranial US
- Death/PVL on 35-42 week cranial US
- Death/abnormal MRI at 35-42 weeks

Secondary outcomes will include

- cerebral palsy
- BSID MDI<70
- BSID PDI<70
- Neurodevelopmental impairment (NDI) defined as any of the following: deafness, blindness, moderate-severe cerebral palsy, or BSID II MDI or PDI score <70.

Bivariate analyses: Analyses of frequency of primary outcomes with respect to SUPPORT treatment groups will be undertaken. Comparisons will be made between ventilation strategy groups (Early CPAP and Control groups) within each randomized oxygenation group, and between oxygenation strategy groups (Low and High SpO2) within each randomized ventilation group. Continuous measures will be compared using the Student t-test and ANOVA where appropriate, and Chi-square analysis will be used to compare categorical data. These analyses would also adjust for the clustering effect introduced by randomizing by week of study.

Sample size and power issues:
Overall GDB and follow-up patient numbers: For year 2003, 1468 infants 24+0 to 27+6 weeks EGA were enrolled in GDB. Of those, 1249 survived to >7 days and 1209 survived to >=14 days. 1027 patients survived to hospital discharge. In year 2003, a total of 725 former 24+0 to 27+6 week EGA patients completed neurodevelopmental assessment at 18-22 months corrected age.
Frequency of neuroimaging outcomes:
Ultrasound: For year 2003, among infants 24+0 to 27+6 weeks EGA surviving to >=14 days, the frequency of Grade 3/4 IVH on cranial US was 20.3%; for those surviving to

discharge it was 18.6%. The frequency of PVL among those surviving to discharge was 3.9%.
MRI: "Abnormal" conventional MRI results among preterm infants at near term are much more difficult to quantify. This is due both to a paucity of available data in the literature, and disparate methods of reporting and scoring "abnormalities" on brain MRI among preterm infants. Two recent studies have attempted to estimate the frequency of white matter signal abnormality, as well as other abnormal findings. Inder and colleagues (47) reported on findings of brain MRI performed at term equivalent age in 100 infants of 23-32 weeks EGA. Only 36/100 were considered to have no white matter signal abnormality, whereas 16/100 had extensive severe white matter signal abnormality. Cortical gray matter abnormalities were rare, with 96/100 patients categorized as normal. Lateral ventricle size was normal in only 40/100. Miller, et. al. (48) reported on MRI findings of 32 consecutive preterm infants, but imaging was performed at earlier postconceptual ages. In addition, previous studies by Maalouf (27) found that 12/19 (63%) preterm infants studied by MRI at 38-44 weeks PCA had abnormal white matter signal, but of those only 7 were moderately to severely abnormal (37%). Childs (30) found 29 of 105 preterm infants (<37 weeks) had abnormal periventricular white matter on MRI, and an additional 5 infants with other abnormalities (32% abnormal). However, the age at the time of MRI in that study ranged from 1-42 days, and PCA at time of scan was not reported. Counsell, et. al. found that, among preterm infants at near term, 34 of 50 had "overt" white matter abnormality or diffuse excessive high signal intensity white matter abnormalities (68% abnormal) (39). In summary then, the frequency of "abnormal" brain MRI in preterm infants ranges from 32-68%. One projected benefit from this proposed secondary study, in fact, would be that the frequency of specific MRI abnormalities in a large premature group could be better clarified and described. For the purposes of sample size and power calculations for this proposal, a conservative estimate of 40% white matter abnormality by MRI at 35-42 weeks will be used.

Thus, the following are the estimated rates for four major outcomes examined in this proposal:

I) Death/Grade 3/4 IVH (14 day)	34.2%
II) Death/Grade 3/4 IVH (at d/c, an estimate of 35-42 weeks)	42.9%
III) Death/PVL (at d/c, an estimate of 35-42 weeks)	32.8%
IV) Death/MRI abnormality	58%

Sample size and detectable difference estimates if all centers could participate:
The revised projected sample size required for SUPPORT is 1310 patients (or 328 patients per each of 4 treatment groups). It is clear that not all Network centers have the neuroradiology personnel or technology in place to participate in the entire proposed study. However, according to the NICHD Neonatal Research Network Brain Imaging Survey, 12 of the 14 Networks centers that responded do have conventional brain MRI capability. Thus, a substantial part of the Network could participate in the conventional MRI portion of this proposed protocol. Using an estimate of 80% enrollment in the cranial US/conventional MRI portion of this proposed secondary, 1048 patients would be enrolled. This would provide an estimated 262 patients in each for 4 groups, such that bivariate comparisons will be made between ventilation strategy groups (Early

CPAP vs. Control ventilation groups) within each randomized oxygenation strategy, and between oxygenation strategy groups (Low vs. High SpO2) within each randomized ventilation strategy.

Thus, for the outcome of Death/Grade 3/4 IVH (14 day), using an expected prevalence rate of 34.2% (see above), a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	33.9% = 34.2% to 22.6%
% increase from expected	35.9% = 34.2% to 46.4%

For the outcome of Death/Grade 3/4 IVH (35-42 week), using an expected prevalence rate of 42.9%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	28.4% = 42.9% to 30.7%
% increase from expected	29.4% = 42.9% to 55.4%

For the outcome of Death/PVL by cranial US (35-42 week), using an expected prevalence rate of 32.8%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	34.4% = 32.8% to 21.5%
% increase from expected	36.9% = 32.8% to 44.9%

For the outcome of Death/MRI abnormality (35-42 week), using an expected prevalence rate of 58%, a projected sample size of 262 patients in each group, alpha 0.05, power 0.8, the following would be detectable:

% reduction from expected	21.6% = 58% to 45.5%
% increase from expected	20.7% = 58% to 70%

The detectable differences were also calculated for an alpha of 0.01 to adjust for the four primary outcomes. Thus,

For the outcome of Death/Grade 3/4 IVH (14 day), using an expected prevalence rate of 34.2% (see above), a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	40% = 34.2% to 20.5%
% increase from expected	43.2% = 34.2% to 49%

For the outcome of Death/Grade 3/4 IVH (35-42 week), using an expected prevalence rate of 42.9%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	33.6% = 42.9% to 28.5%
% increase from expected	35.2% = 42.9% to 58%

For the outcome of Death/PVL by cranial US (35-42 week), using an expected prevalence rate of 32.8%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	40.2% = 32.8% to 19.6%
% increase from expected	42.7% = 32.8% to 46.8%

For the outcome of Death/MRI abnormality (35-42 week), using an expected prevalence rate of 58%, a projected sample size of 262 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	25.8% = 58% to 43%
% increase from expected	24.8% = 58% to 72.4%

If MRI could not be performed in all sites due to budgetary constraints, clearly differences between groups with respect to the outcome of Death/MRI abnormality would need to be larger in order to detect. If the number of patients involved in the MRI portion of the proposed study were reduced by one-half (to 524), then the sample size per group would drop to 131. In that case:

For the outcome of Death/MRI abnormality (35-42 weeks), using an expected prevalence rate of 58%, a projected sample size of 131 patients in each group, alpha 0.01, power 0.8, the following would be detectable:

% reduction from expected	37% = 58% to 36.5%
% increase from expected	35.5% = 58% to 78.6%

However, the estimate of 40% white matter abnormality on MRI among preterm infants at term is conservative, thus the estimate of 58% for the outcome of Death/MRI abnormality may also be low.

Regression Analyses: In addition to bivariate analyses, regression analyses will be undertaken to attempt to adjust for confounding variables in comparisons of treatment groups with respect to neuroimaging findings. The independent association of ventilation strategy will be determined for each neuroimaging outcome (Grade 3/4 IVH at 7-14 days, 35-42 weeks, PVL at 35-42 weeks, MRI abnormality), adjusting for gestational age, weight, and oxygenation strategy. Similarly, the independent association of oxygenation strategy will be determined for each neuroimaging outcome (Grade 3/4 IVH at 7-14 days, 35-42 weeks, PVL at 35-42 weeks, MRI abnormality), adjusting for gestational age, weight, and ventilation strategy.
Neurodevelopmental Outcomes Logistic Regression Models: We propose a novel approach to the comparison of neuroimaging modalities with respect to neurodevelopmental outcomes, that of logistic regression modeling. Numerous

neurodevelopmental outcomes studies have used this approach, however previous studies of brain MRI in the premature infant have lacked the sample size to implement this statistical technique. Models will be developed to include perinatal, demographic, neonatal and socioeconomic factors pertinent to neurodevelopmental outcome as demonstrated in previous reports (14,15) and the univariate and multivariate analyses carried out. Neuroimaging study results (cranial US at 7-14 days, cranial US at 35-42 weeks PMA, and brain MRI at 35-42 weeks) will be added to the model individually and in combination, to determine the adjusted risk for adverse outcome that each imparts, and to ascertain if any two abnormal studies (i.e., early cranial US and MRI, or early and late US) are materially more predictive of neurodevelopmental impairment than any single abnormal study. Ventilatory strategy and oxygen saturation strategy will also be available as crucial neonatal factors that may impact on outcome.

Predictive modeling of outcome: Challenges to the development of a predictive model include the need for both a "model development" data set and a "model validation" data set. Possible solutions to this challenge include splitting the proposed study data set in half, thus creating a development and validation set; or by employing a so-called "boot-strapping" technique by which multiple random samples of the data set are used for calculating confidence intervals for predictions (49). Further analysis will be required to determine the best strategy for predictive modeling in the proposed study.

Further Statistical considerations: Development and comparison of predictive models:

I. Initial model development, the models and their variables.

The sample will be randomly split into a development dataset with 50% of cases and 50% of controls and a test dataset with 50% of cases and 50% of controls. Several models will be developed of which the following are projected to be central models; however, additional models may also be developed:

1. "Classic" risk model, including traditional factors (i.e., gestational age, birth weight, gender, race, maternal education, etc.) as well as "worst" early cranial US
2. Late cranial US model
3. Conventional MRI model

For each model, the number of categorical variables will be restricted to 5 – 10 observations per category cell. When candidate variables exceed this ratio, the best set of significant predictor variables will be chosen by forward selection. In this case, at each step the variable with the most significant effect will be identified and added to the model. The same dataset will be used for the development of each model.

II. Model calibration and goodness-of-fit

Each model will be calibrated using Pearson chi-square, likelihood ratio chi-square, and Hosmer and Lemeshow statistic.

III. Model discrimination and predictive ability

Sensitivity (true positive rate) and specificity (true negative rate) of the models to predict outcome will be evaluated. The receiver-operator curve (ROC) will be used to display model discrimination by plotting sensitivity against specificity. The predictive abilities of

the models will be compared using area under the curve (AUC) analyses (Hanley JA and McNeil BJ, *Radiology* 1982)

IV. Multidimensional model.
Finally, we will attempt to build a model that combines the most significant factors from cranial US and MRI models and compare to the above models.

Potential ancillary analyses:

1) Modeling "normal neurodevelopmental outcome": The majority of published neurodevelopmental outcomes analyses in the ELBW population focus on significant neurodevelopmental impairments as primary outcomes. The proposed study could use logistic regression modeling to include analysis of the adjusted risk for "normal outcome" imparted by "normal" neuroimaging studies. This approach would further delineate the relative importance of each imaging modality in terms of their predictive capabilities.
2) Cost effectiveness of MRI at 35-42 weeks PMA: If the hypotheses are proven, abnormal results of brain MRI will be shown to be more strongly independently associated with adverse neurodevelopmental outcome than abnormal cranial US findings. However, the cost effectiveness of MRI will be important to determine before wide-scale implementation of new neuroimaging modalities can be recommended. To this end, analyses could be undertaken that would estimate the cost for each additional adverse outcome predicted; this approach would be conceptually similar to a "number needed to treat" analysis. Dr. Jon Tyson, has extensive experience in analyses of resource use and evaluation of costs (50,51) and would play an essential role in developing effective strategies to evaluate this question.

APPENDICES

Appendix A: Magnetic resonance imaging requirements and image acquisition
Conventional MRI: Network centers that have any "type" of device (i.e., GE, Philips, Siemens, etc.) capable of performing standardized conventional neonatal brain MRI sequences with 4 mm contiguous slices (0mm gap) will be able to participate. All examinations will include conventional fast spin echo (FSE) T1-weighted and T2-weighted sequences as well as fluid attenuated inversion recovery (FLAIR) and gradient echo (GRE) sequences.

Appendix B: Medical instability at 35-42 week PMA MRI
For "medical instability" to be considered the cause of non-acquisition of MRI, one of the following conditions should exist during the entire 35-42 week PMA MRI imaging window:

- The patient is intubated.
- The patient is considered by the attending neonatologist to be critically unstable such that transport to the radiology suite would be unsafe.

Appendix C: Definitions

Early Cranial Ultrasound:

- Grade I: blood/echodensity in the germinal matrix/subependymal area
- Grade II: blood/echodensity in the lateral ventricle without distention
- Grade III: blood/echodensity in the lateral ventricle with distention
- Grade IV: blood/echodensity in the parenchyma
- Cystic areas in the parenchyma: cystic areas in the parenchyma associated with a Grade IV IVH

Late Cranial Ultrasound

- See definitions above
- Cystic periventricular leukomalacia: cystic areas in the parenchyma in the absence of a parenchymal hemorrhage.
- Porencephalic cyst
- Presence of shunt

Conventional MRI interpretation and scoring:

NOTE: Adjustments and amendments to the following scheme may be made after further discussion and input from members of the Steering Committee and SUPPORT Subcommittee.

- C1 = normal
- C2 = minimal subependymal hemorrhage or mineralization with no or mild ventriculomegaly
- C3 = moderate to severe ventriculomegaly
- C4 = parenchymal abnormality
- C5 = periventricular cystic abnormality
- C6 = white matter signal abnormality
- C7 = increased extra-axial fluid
- C8 = cerebellar hemorrhage or mineralization
- C9 = diffuse excessive high intensity signal

Cerebral Palsy ("Neonatal Research Network Follow-Up Study Manual of Operations")
Cerebral palsy at 18-22 months will be diagnosed if definite findings are encountered on exam in any two of the following three areas:

1) Delay in motor milestones – determined using the motor quotient as described in the Manual of Operations.
2) Abnormalities obersed in the classical neuromotor exam, which includes measurement of tone, deep tendon reflexes, coordination and movement (not including eye movement). Any one abnormality, except for isolated low tone or toe walking is sufficient.
3) Aberrations in primitive reflexes and postural reactions – any aberration is sufficient.

Cerebral palsy will be further categorized by type and severity, as described in the Manual of Operations.

Human Subjects
1. Risks to the subjects:

a) Human Subjects Involvement and Characteristics: Infants enrolled in the NICHD Neonatal Research Network SUPPORT trial will be recruited. Inclusion and Exclusion criteria have been defined as stated in the Research Plan. The final population will be dependent upon the number of sites within the Network that participate in this study. Both male and female infants will be enrolled. We expect the study population to be representative of the racial background and gender distribution of the Neonatal Research Network. In 2001, 49% male and 51% female patients constituted the ELBW population of the Neonatal Research Network, of which 43% were black, 38% were white, 15% were hispanic, and 3% were other races.
b) Sources of Materials: Sources of research material will consist of perinatal, demographic and neonatal data collected by research personnel as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality Among VLBW Infants (401-1500 g), and through the data collection mechanisms associated with the SUPPORT trial. Additional data will be obtained through evaluation of brain MRI images by a central reader masked to all patient identifiers and patient outcomes. Data forms will be created, completed by the central MRI reader, and submitted to Research Triangle Institute per protocol. Neurodevelopmental outcome data will be obtained from the NICHD Neonatal Research Network Follow-up Study of ELBW Infants, and per SUPPORT specifications.
c) Potential Risks: The risks and discomforts of participation are minimal as the study relies primarily on data collected for ongoing studies already in progress, and uses non-invasive techniques. Cranial US is performed routinely in all NICU's in the NICHD Neonatal Research Network, is considered standard of care, and techniques would not be altered by this study. Brain MRI at 35-42 weeks postmenstrual age is already routine in several Network centers. Sedation will not be used routinely, although may be used particularly in centers that already do use sedation. Temporary minor skin irritation from tape used to apply MRI-compatible monitoring electrodes may occur, but this risk is unlikely. Temporary transport of a patient to a radiology suite for MRI may also represent a possible risk; however, only those patients considered stable for transport will undergo imaging, and a 7- week window of opportunity for MRI is built into the proposed study. The alternative to obtaining a brain MRI as part of the proposed study is non-enrollment.

2. Adequacy of Protection Against Risks:
a) Recruitment and Informed Consent :
Screening: The individual center will be responsible for devising a screening strategy to identify all potential participants using the study inclusion and exclusion criteria. Screening, identification and informed consent procedures should be completed by 14 days of age as "early cranial US" must be performed by this time.
Informed consent: Each participating center will follow procedures for developing informed consents as set out by their Institutional Review Board (IRB). The parents of all infants enrolled in SUPPORT will be approached to participate in this secondary study, and informed consent must be obtained by the individual center. Informed consent will be obtained by the Principal Investigator or his/her designee.
Eligible infants not enrolled: The reasons for non-enrollment of eligible infants will be documented. Short- and long-term outcomes of eligible infants not enrolled in this study

will be documented as part of the NICHD Neonatal Research Network Survey of Morbidity and Mortality in Very Low Birth Weight (VLBW) Infants (Generic Data Base (GDB)) and, if enrolled, as part of the ongoing NICHD Neonatal Research Network ELBW Neurodevelopmental Follow-Up Study.
No MRI obtained for enrolled infants: The objective of the proposed study requires acquisition of cranial US and MRI at 35-42 weeks PMA; if the patient is deemed medically unstable during the entire 35-42 week PMA period, an MRI will not be obtained. Other reasons for inability to obtain the MRI will also be documented.
b) Protection against risk: Every effort will be made to protect study patients from potential risks of participation. Stability of study patients for transport to a radiology suite for brain MRI will be assessed by the attending neonatologist at each participating site. Should a patient be judged to be unstable for transport to the radiology suite, a 7-week window of opportunity for MRI (35-42 weeks postmenstrual age) has been provided in the protocol. Any adverse events with regard to obtaining neuroimaging studies among enrolled patients will be documented and submitted to NICHD, the data center, and the local IRB. The NICHD Neonatal Research Network has an independent Data Safety Monitoring Committee (DSMC), which would provide continuous oversight of patient safety and risk factors for the duration of the study. The DSMC will review the study on at least an annual basis.

3. Potential Benefits of the proposed research to the subjects and others: The potential benefits of participation to an individual patient include identification of structural anomalies by MRI that would not have been identifiable by ultrasound. This may allow for early, targeted intervention for the individual patient that otherwise would not have been undertaken. Other potential benefits would be to future extremely preterm patients after results of this prospective study are known (see below).

4. Importance of the knowledge to be gained:
Provide a thorough neuroimaging monitoring arm for SUPPORT: Although cranial US is a standard diagnostic procedure in the NRN, the proposed study would provide a framework for specifically timed cranial US studies, which would be more appropriately comparable. In addition, subtle but arguably extremely important findings consistent with brain injury would be detectable by MRI.
Counseling, follow-up: Detection of an injury pattern which is consistent with later neurodevelopmental delay will be useful for counseling and targeted, early follow-up. Identifying such a tool would provide a link to later research in early intervention.
Clarify the pathogenesis of injury leading to neurodevelopmental impairment: Further delineation of pathophysiologic correlates of later outcome could possibly be linked with perinatal and neonatal factors, which would 1) focus future research and intervention on clinical events associated with the pathophysiologic hallmark, 2) provide important data leading to further study of the pathogenesis and timing of injury, and 3) assess neuroanatomic localization of subtle injury associated with later neuromotor abnormalities.
Contribution to the literature with respect to diagnostic strategies for the extremely preterm population: Previous neuroimaging practice parameters have concluded that insufficient evidence exists to recommend advanced neuroimaging for premature infants

for prediction of neurodevelopmental outcomes. The proposed study would address this significant gap in the collective literature.

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DATE: August 19, 2004

TO: Susan Hintz, MD

FROM: Richard A. Ehrenkranz, MD
Chair, Protocol Review Subcommittee

RE: Neuroimaging and Neurodevelopmental Outcome: A SUPPORT Trial Secondary Study (24Jun04 version)

The Protocol Review Subcommittee reviewed this secondary study during its conference call on August 18, 2004; reviews and comments were prepared by Jon Tyson and Dale Phelps; copies of those reviews are attached below.

This revised proposal addresses many of the critiques made in the Subcommittee's review of the December 2003 version of this proposal. We were especially enthusiastic that the project was now a secondary study to the SUPPORT Trial, and believed that this linkage would be a "win" for both projects. We noted that, compared to the December 2003 version in which both conventional and DTI MRI studies performed at 36-42 weeks PMA were to be compared to a cranial ultrasound obtained within 7 days of the MRI studies, the revised proposal will only compare the conventional MRI with the cranial ultrasound. Since the previous version suggested that DTI studies might be better than either conventional MRI or cranial ultrasound in identifying white matter injury, the Subcommittee questioned the appropriateness of the new study design. We appreciate that addition of a DTI scan adds to the length of the MRI study and increases the likelihood that sedation would be required, and we appreciate the problems (eg, IRB, consent, patient recruitment) that would result if sedation were needed. Please note that some of the comments in the attached reviews relate to confusion about this design change.

Other issues discussed included:

1. The wording of the hypotheses: The primary hypotheses stated in the December 2003 version related MRI findings to neurodevelopmental outcome. In the revised proposal, the relationship to neurodevelopmental outcome is a secondary hypothesis and the primary hypotheses focus on the relationship between Death/Grade 3/4 IVH and between Death/PVL and the assigned study group. We suggest that the primary hypotheses be restated and focus on the relationship between neuroimaging findings at 35-42 weeks PMA and neurodevelopmental outcome. Since the number of infants in each study cell of the SUPPORT trial that participate in this secondary trial might vary, the relationship between study intervention and neuroimaging finding should probably be secondary hypotheses. Given the comments above, more justification about the study design change should be provided. If DTI findings turn out to be the best predictor of neurodevelopmental outcome, then this project will be studying the wrong technology. Perhaps this study should only be done by those centers that have DTI scanners. Or perhaps, some centers should compare late cranial ultrasound with conventional MRI and others cranial ultrasound with DTI. The responses to the recent questionnaire should help to identify the resources available and the practices (sedation vs "feed and wrap") at the network centers.

2. Early cranial ultrasound: What is the importance of the early cranial ultrasound to this project? Early cranial ultrasound studies are obtained clinically, define the extent of IVH, and resolution vs the development of post-hemorrhagic hydrocephalus. For infants with multiple studies between day 7-14, which scan will the "study " ultrasound? These data will be collected in the GDB and as part of the SUPPORT trial database and can be used in this project's analyses. As suggested

above, why not focus this project at the relationship between neuroimaging findings at 35-42 weeks PMA and neurodevelopmental outcome?

3. Sedation

4. Cost of the secondary study: The scenarios provided with the estimated budget discussion were great, but we felt that a budget estimate based upon the results of the recent questionnaire would be more accurate.

5. The performance of a cost-effectiveness study would be interesting. However, that project would need to be specifically designed to insure that sufficient data are collected during the performance of this project.

6. Justification of central readers. (Seetha noted that there is no standard neuroimaging description of PVL and suggested the following reference: Holling and Leviton; Characteristics of cranial ultrasound white matter echolucencies that predict disability:a review; Devel Med Child Neurol 1999:41:136-139).

Overall, the Subcommittee likes this proposal and thinks that it is an appropriate SUPPORT Trial secondary study. However, we believed that the hypotheses should be restated and that the design and budget estimate should be revised with the information collected by the recent questionnaire. Therefore, we did not think that this proposal was ready to be submitted to the Steering Committee for consideration.

Review submitted by Jon Tyson (prepared July 30):

Primary Hypotheses and Specific Aims

Hypothesis 1- It would be good to be a bit more specific; I would suggest you add the words "performed at the same age" or "performed within the same week."

Hypothesis 2 – Why not modify this hypothesis to something like "The evaluation of DTI , specifically..., in performing MRI will allow cerebral palsy and neurodevelopmental morbidity to better predicted than from the findings of conventional MRI alone." I suggest this hypothesis, in part because of your preliminary work.

The third hypothesis seems too vague for my tastes, and I have a hard time accepting two "primary" hypotheses, much less three, rather than one.

You could add a secondary hypothesis or specific aim like "The use of MRI will be cost effective in increasing the prediction of cerebral palsy and neurodevelopmental outcomes." No one will be surprised if MRI augments the prediction of outcome; the question is whether it is worth the incremental resource costs. Cost effectiveness could assessed based on detailed estimates of resource costs in a few interested centers and expressed as extra cost per extra infant whose outcome could be correctly predicted or per extra infant with cerebral palsy or neurodevelopmental morbidity. If you are interested, I can help you in defining how to assess this.

Ref aim 6 You should refer to prognostic validity rather than prognostic utility since strictly speaking you are not going to measure utility.

Methods

Local vs Central readings. In assessing the prognostic validity of MRI and sonography as they will be used in the real world, local readings for both should be used. (In comparing the predictive validity of MRI to sonography, it would not be appropriate to compare local sonographic readings to central MRI readings.) Central readings for MRI are of interest if you want to compare the reliability of local readings against "gold standard," to assess the pathophysiology of white matter disease and it is crucial to have the most accurate possible assessment, and to rigorously assess the effect of therapeutic interventions in clinical trials like Support, Inositol, whatever. What will be gained, of course, has to be weighed against the cost and effort required.

Sedation. You might want to expand the protocol or provide more information outside the protocol about methods to minimize the need for sedation using head coils, feeding, swaddling, or whatever. (Like you, Nehal Parikh has been looking into this in our center and has been able to reduce the proportion of infants deemed to need sedatives. You two might want to talk.) The risks and benefits of sedation need to be place in the context of other uses of sedation in the neonatal period. (I am surprised by neonatologists who use sedation and narcotics so freely in the NICU with little or no evidence of therapeutic benefit but yet object to a single low dose administration to infants at lower risk in order to obtain diagnostic and prognostic benefit.)

Sample size. As I understand your sample size calculation, it is based on the number of babies who could be studied rather than the number who need to be studied. I wonder if you couldn't use a smaller number of patients to address your primary hypotheses and have a much less expensive and more feasible study. You might ask Nehal for a copy of his K23 proposal (priority score 158!) to see how we approached the sample size calculation in proposing to study the relationship of volumetric MRI to outcome.

Pilot study. Carefully consider whether you should propose a pilot study before preparing the final protocol and defining the sample size and expected duration of study. It seems like there are too many loose ends.

Budget. Sorry but I haven't had time to review the budget but I wanted to ask if you have included the cost of the 2nd sono for centers like ours that do MRIs instead.

Review submitted by Dale Phelps:

Opinion:

This is an interesting study that will provide needed data for the care of preterm infants in the future. It is non-therapeutic, but will determine the best testing to be done prior to discharge to enable infants to be identified for early intervention treatments. The results will guide the evolving standard of care for preterm infants.

In addition, as a secondary to SUPPORT, it will enhance the outcome evaluation of the SUPPORT study. There will be data near term on infants who otherwise fail to return for follow up, and this surrogate outcome may prove to be helpful if the remainder of the study hypotheses show that MRI is useful in prediction of outcomes at 18-22 months.

I have moderate enthusiasm for the study, but serious concerns about the costs. Perhaps co-funding with Neuro institute, or a Radiologic foundation would be feasible?

Protocol Summary:

This protocol is a resubmission and originally was intended to stand alone and be conducted in just two centers. Is has now been revised and is submitted as a secondary study, attached to the SUPPORT trial which will entail a great deal more involvement of the network centers.

This study primarily seeks to determine if MRI near term is a better predictor of neruodevelopmental outcomes than ultrasound near term. In addition, they ask the same question of diffusion tensor imagine (DTI/MRI). They will also compare these to determine if they are better predictors than early ultrasound or the combination of early and near term ultrasounds. (That's six related questions).

Because the population of the SUPPORT study is the one of gestational age interest, they propose to conduct the study as a secondary to the SUPPORT study with the additional advantage that they will be able to compare the outcomes of the infants with the best of these testing modalities (any and all of them) across the 2x2 factorial randomization resulting in 4 groups of interest (but two interventions).

The protocol calls for the clinically usual early ultrasound to be done at 7-14 days. Then near term (35-40 weeks) that both an ultrasound (usual in some centers) and MRI (usual practice in the other centers) be accomplished. In addition, selected centers would also obtain DTI at the time of the standard MRI.

Critique:

We have previously reviewed this proposal and the authors have responded to concerns with a revised protocol. The gestational window of 'near term' has been extended down to 35 weeks. By becoming secondary to the SUPPORT trial, greater detail on blood gases and oxygen exposure will be available at no additional expense. In addition, by becoming secondary to the SUPPORT trial, the concerns about sample size have been addressed, although the power to detect predictive power from the DTI will remain unspecified until the number of participating centers able to comply with study standards for DTI is determined.

The authors should consider the effect on this protocol, if enrollment in the SUPPORT trial is stopped early.

The central reading centers will be expensive, as will the costs for the participating centers to arrange copies and transport of the ultrasound and MRI files. However, I am persuaded by the arguments that this is necessary. It may, in fact, prove to be prohibitive. The authors should consider if radiology investigators would consider participation as co-authors and therefore provide their time reading the studies at a low rate.

The budget estimate is necessarily complex and fluid as individual centers are in various stages of changing over from ultrasound to MRI as their usual modality. In addition, there is yet no estimate of the costs for the reading centers. Therefore it is not possible to judge the cost of this protocol.

We have used 2003 data provided by RTI (see proposal, "Sample Size and power issues") to estimate the number of patients likely to be eligible for participation in this proposed secondary, and subsequently, the number of neuroimaging studies that may be performed. Survival to >7 days for 24 to 27+6 week EGA infants was 85%. Among those surviving >7 days, 82% survived to discharge. With the revised sample size for SUPPORT of 1310, this would result in approximately 1114 infants available for 7-14 day neuroimaging studies, and 913 infants available for 35-42 week neuroimaging studies.

1) Extent of participation in proposed secondary: It is understood that the extent of participation in this proposed secondary is not yet clear. Budgetary considerations may limit the extent of sites able to participate in the full secondary. In the most fiscally conservative situation, only those sites currently or soon to be performing routine brain MRI at near-term would obtain all neurodiagnostic studies. However, given the primary goal of this secondary (providing a safety arm to SUPPORT), it would be appropriate for all NRN sites to participate in early and late US collection. Since the publication of the neonatal neuroimaging practice parameter (Neurology 2002), it is likely that all NRN sites have implemented routine cranial US at 7-14 days and at near-term as standard of care. A survey of practices will be sent to Network PI's.

We have provided an estimate of absolute requirements, as well as possible enrollment scenarios.

2) Requirements for study, regardless of the level of participation in the proposed secondary:

- Cranial US central reading: This would include costs for shipping of films or CD's, and for radiologist(s) time to interpret both "early" (7-14 days) and "late (35-42 weeks) cranial US. If 80% enrollment for this cranial US portion were to be achieved, this would result in 891 "early" US and 731 "late US = 1622 studies.

  The NICHD NRN is currently in the process of central reading for cranial US associated with the PiNO trial. Therefore, costs associated with central reading may be estimated from that experience (Dr. Rose Higgins to comment).

- Conventional MRI central reading: This would include costs for shipping of films or CD's, and radiologist(s) time to interpret conventional 35-42 week MRI. Total number of studies would depend on the level of restriction of enrollment due to budgetary considerations.

  The NICHD NRN is embarking upon central reading of MRI associated with the Hypothermia trial. Therefore, costs may be estimated with the input of Dr. Rose Higgins.

3) Costs for 7-14 day cranial US:

Because 7-14 day cranial US should be considered a "standard of care" routine in NICU's, no additional costs will be incurred apart from shipping/central reading as described above.

4) For centers with 35-42 week brain MRI already a "standard of care" routine":
If centers already performing MRI at near-term were to participate in the cranial US/MRI portion of the proposed secondary, *the additional cost of a 35-42 week cranial US would be the only additional cost incurred*, since those centers are unlikely to obtain both MRI and cranial US at near-term. Each network center will have a negotiated NIH reimbursement cost for each neuroimaging study; at Stanford, the negotiated cost of a cranial US is $210.29.

A survey of practices will be distributed to address how many Network centers *currently routinely* perform near-term brain MRIs.

5) For centers that do not routinely perform brain MRI at near-term:
If centers performing cranial US at near-term *were* to participate in the cranial US/MRI portion of the proposed secondary, *the additional cost of a 35-42 week brain MRI would be incurred*. At Stanford, the negotiated cost for a non-contrast brain MRI is $906.60.

However, if budgetary considerations were to prevent participation in the MRI portion of this secondary, these sites could participate in data collection with respect to cranial US findings. This approach would incur no additional neuroimaging costs for these sites.

Therefore, the total cost of additional neuroimaging for this proposed secondary will be dependent upon the proportion of enrolled patients requiring cost coverage for brain MRI vs. "late" cranial US. Each participating center will be required to submit a budget.

Scenario #1: The following are estimated costs for "late" US and conventional brain MRI based on 80% enrollment in the **full** neuroimaging study (731 patients), using Stanford negotiated costs, and assuming varying proportions of patients requiring cost coverage for brain MRI/cranial US as follows:

a) 10% of patients require brain MRI cost coverage/90% require "late" cranial cost coverage:

brain MRI cost	cranial US cost
0.1 x 731 = 73	0.9 x 731 = 658
76 x $906.60 = $66,181.80	658 x $210.29 = $138,370.82

Total cost for 35-42 week US/conventional MRI for this scenario: $204,552.62

b) 30% of patients require brain MRI cost coverage/70% require "late" cranial cost coverage:

brain MRI cost	cranial US cost
0.3 x 731 = 219	0.7 x 7 = 512
219 x $906.60 = $198,545.40	512 x $210.29 = $107,668.48

Total cost for 35-42 week US/conventional MRI for this scenario: $306,213.88

Scenario #2: Estimated costs for "late" US and conventional brain MRI based on limiting enrollment in the **full** neuroimaging study to 50% (457 patients), using Stanford negotiated costs, and assuming varying proportions of patients requiring cost coverage for brain MRI/cranial US as follows:

a) 10% of patients require brain MRI cost coverage/90% require "late" cranial cost coverage:

brain MRI cost	cranial US cost
0.1 x 457 = 46	0.9 x 457 = 411
46 x $906.60 = $41,703.36	411 x $210.29 = $86,429.19

Total cost for 35-42 week US/conventional MRI for this scenario: $128,132.55

b) 30% of patients require brain MRI cost coverage/70% require "late" cranial cost coverage:

brain MRI cost	cranial US cost
0.3 x 457 = 170	0.7 x 457 = 320
170 x $906.60 = $154,122.00	320 x $210.29 = $67,292.80

Total cost for 35-42 week US/conventional MRI for this scenario: $221,414.80

Scenario #3: Estimated costs for "late US" ONLY based on limiting enrollment to only those sites where brain MRI is currently or will be routinely undertaken for near-term imaging, using Stanford negotiated costs. The following are projections ONLY, since the total number of sites currently or soon to be performing routine brain MRI is not yet clear:

a) If 30% of the patients enrolled in SUPPORT would routinely undergo near-term brain MRI and participated in this secondary -

brain MRI cost	cranial US cost
$0	274 studies x $210.29 = $57,619.46

Total cost = $57,619.46

b) if 50% of the patients enrolled in SUPPORT would routinely undergo near-term brain MRI and participated in this secondary –

brain MRI cost	cranial US cost
$0	457 studies x $210.29 = $96,102.53

Total cost = $96,102.53

Scenario #4: Depending on budgetary considerations, it may be possible for SOME centers that are not currently performing routine near-term brain MRI to participate in this secondary. This involvement would be limited to highly motivated and interested

sites, and would require reimbursement for MRI studies. An example of this would be the following:

If 30% of the patients enrolled in SUPPORT would routinely undergo near-term brain MRI and participated in this secondary, cost for those patients would be for cranial US only as shown above (Scenario #3 (a) = $57,619.46). If, in addition, 50 patients from highly motivated centers where MRI was NOT routinely performed at near-term wished to participate, the projected cost would be for MRI reimbursement = 50 x $906.60 = $45,330.00 (using Stanford negotiated costs as estimates). Thus, the total neuroimaging costs would be = $102,949.46

From:	Neil Finer
To:	"Wally Carlo, M.D."; Higgins, Rosemary (NIH/NICHD) [E]; "Edward Donovan"; sduara@miami.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu
Cc:	poo@rti.org; "Alan Jobe (E-mail)"
Subject:	RE: enrollment
Date:	Friday, September 24, 2004 4:14:08 PM

Let's Discuss in DC

Sounds OK to me

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, September 24, 2004 8:37 AM
To: Higgins, Rosemary (NIH/NICHD); Edward Donovan; sduara@miami.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
Cc: poo@rti.org; Alan Jobe (E-mail)
Subject: RE: enrollment

I think this is a great idea. The incidence of the outcomes and effect size probably differ by subgroup which would affect the sample size but there are so many variables that affect these, that I would expect that if the learning curve period is kept short, the effects will be trivial and largely unpredictable at this time. Any way, we are making a lot of assumptions. Making one minor one should not have a large impact. Wally

---

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 24, 2004 10:25 AM
To: 'Edward Donovan'; sduara@miami.edu; Wally Carlo, M.D.; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
Cc: 'poo@rti.org'; Alan Jobe (E-mail)
Subject: RE: enrollment

I think I had talked to Alan about this at the training in informal discussion. I think it is definitely a great point to bring up with the subcommittee and then again Tuesday with the Steering Committee. If a "non-CPAP center" starts with a 24 0/7 week infant and fails, it may hamper ability to recruit. If they start with a 27 4/7 week baby and are able to adhere to the protocol, this may instill some needed confidence to then "lower the GA bar." We need to be cognizant of current practice versus implementation of the protocol and work with each site to meet their needs. We also need to find out if there are statistical considerations if we "over recruit" the bigger babies earlier. Any other thoughts??

> -----Original Message-----
> **From:** Edward Donovan [mailto:Edward.Donovan@cchmc.org]
> **Sent:** Friday, September 24, 2004 11:18 AM
> **To:** Edward Donovan; Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
> **Subject:** enrollment
>
> I heard through the grapevine that Alan suggested we consider staggered enrollment by GA group, i.e. allowing centers to start with the 26-27 week group first if they wanted.
> Part of the rationale was that some centers are quite comfortable with early and prolonged CPAP

for these "bigger" babies, but not so comfortable with the 24-25 weekers.
This might help address the "learning curve" issue.
I think that this idea is worth discussion?
Ed

Edward F. Donovan, M.D.
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Children's Hospital Medical Center
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Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

From: Wally Carlo, M.D.
To: Duara, Shahnaz; aaf2@po.cwru.edu; edward.donovan@cchmc.org; poo@rti.org; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Michele Walsh
Subject: RE: CPAP associated outcomes
Date: Monday, September 20, 2004 10:48:46 AM

I do not think "accidental" extubations will be used for that purpose as they may work! wally

-----Original Message-----
From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Monday, September 20, 2004 9:45 AM
To: Wally Carlo, M.D.; aaf2@po.cwru.edu; edward.donovan@cchmc.org; poo@rti.org; nfiner@ucsd.edu; Rosemary Higgins; Michele Walsh
Subject: RE: CPAP associated outcomes

Dear Wally,

I guess we are saying the same thing, since the extubation/re-intubation criteria are the same. The only difference between our points of view is that, if accidental extubations count towards the total of 2 allowed extubations, then centers who want to go to CPAP at high settings in the control arm just need to 'accidentally' pull the ET tube twice and the baby is out of the vent. part of the study. Wouldn't that be considered allowing an introduction of bias?

Shahnaz

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 20, 2004 8:42 AM
To: 'wcarlo@peds.uab.edu'; Duara, Shahnaz; 'edward.donovan@cchmc.org'; 'poo@rti.org'
Cc: Duara, Shahnaz; 'aaf2@po.cwru.edu'; 'mcw3@po.cwru.edu'; 'nfiner@ucsd.edu'
Subject: Re: CPAP associated outcomes

Hi
I think this is standard practice - good suggestion
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Duara, Shahnaz <SDuara@med.miami.edu>; Edward Donovan <Edward.Donovan@cchmc.org>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; poo@rti.org <poo@rti.org>
CC: Duara, Shahnaz <sduara@miami.edu>; aaf2@po.cwru.edu <aaf2@po.cwru.edu>; mcw3@po.cwru.edu <mcw3@po.cwru.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>
Sent: Mon Sep 20 08:41:33 2004
Subject: RE: CPAP associated outcomes

I am ok to leave the babies who had unplanned extubations off the ventilator unless they meet reintubation criteria as this would be the best medical judgment. Wally

---

From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Friday, September 17, 2004 3:07 PM
To: Edward Donovan; higginsr@mail.nih.gov; poo@rti.org
Cc: Duara, Shahnaz; Wally Carlo, M.D.; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
Subject: RE: CPAP associated outcomes

Good idea.
We also need to clarify the issue of unplanned extubations for the control arm.
My concern is that, if the ventilator settings and most recent blood gas prior to the extubation didn't qualify a baby for trial of extubation, then allowing the baby to stay extubated will create real noise in the data. To avoid multiple extubations and reintubations, every site will need to pay close attention to ET tape jobs, patient positioning and gentle control of hands away from the tube etc, much as we do for routine clinical care.

Shahnaz

-----Original Message-----
From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Friday, September 17, 2004 3:33 PM
To: higginsr@mail.nih.gov; poo@rti.org
Cc: Edward Donovan; Duara, Shahnaz; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu; nfiner@ucsd.edu
Subject: CPAP associated outcomes

Ken and Rose,

Several people asked about the extent to which our aggressive use of CPAP at University Hospital in Cincinnati is associated with other aspects of care. Would it be possible to pull some hospital-specific GDB data for UH? For babies who are 23-27 weeks GA, who have reached status and who were born between January 1, 2001 and the present - as a group (23-27) and by GA and by GA group (24 + 25 and 26 + 27):

births

intubated in DR

any CPAP (duration of CPAP for those who received any CPAP)

any surfactant (overall and for those who received CPAP)

any IMV (duration of IMV for those who received IMV)

LOS (overall, for those who died and for those who survived to 120 days)

I'm copying this to the subcommittee to see if they agree with these analyses.

Thanks,
Ed

Edward F. Donovan, M.D.
Director
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Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

From: Wally Carlo, M.D.
To: Duara, Shahnaz; Neil Finer; edward.donovan@cchmc.org
Cc: Michelle Walsh; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: CPAP script draft
Date: Friday, August 27, 2004 12:36:58 PM

Looks good. With regards to position, we are ok with doing CPAP in all positions. Also, great, concise call. Thanks, wally

---

From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Friday, August 27, 2004 9:10 AM
To: Neil Finer; edward.donovan@cchmc.org
Cc: Wally Carlo, M.D.; Michelle Walsh; higginsr@mail.nih.gov
Subject: RE: CPAP script draft

Hi Ed and Neil,

The text looks fine overall. We don't use the prone position with CPAP, in an effort to avoid torque on the nares, so am looking forward to learning how you position the baby to maintain a seal and keep the nose intact.

Will be on the call at noon EST
Shahnaz

> -----Original Message-----
> **From:** Neil Finer [mailto:nfiner@ucsd.edu]
> **Sent:** Thursday, August 26, 2004 11:07 PM
> **To:** Edward Donovan; Vivek Narendran; higginsr@mail.nih.gov; Duara, Shahnaz; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu; mcw3@po.cwru.edu; pam@savethegonad.com
> **Cc:** Neil Finer
> **Subject:** Re: CPAP script draft
>
> Hi Ed
> Very nice and concise. I have asked a few questions and added some words. Please see if these are value added. Talk to you in the morning.
> Neil
>
> > ----- Original Message -----
> > **From:** Edward Donovan
> > **To:** Edward Donovan ; Vivek Narendran ; higginsr@mail.nih.gov ; sduara@miami.edu ; Wcarlo@peds.uab.edu ; aaf2@po.cwru.edu ; mcw3@po.cwru.edu ; pam@savethegonad.com ; nfiner@ucsd.edu
> > **Sent:** Thursday, August 26, 2004 1:53 PM
> > **Subject:** CPAP script draft
> >
> > Attached is a draft of the CPAP portion of the script. I know that it is difficult to evaluate these scripts without the accompanying video.
> >
> > However, I would like your comments on the content (or lack thereof), style, order in which things are presented, etc.
> >
> > We're moving forward and intend to show the video on Weds. morning of training.
> >
> > Thanks,
> > Ed
> >
> > Edward F. Donovan, M.D.
> > Director
> > Child Policy Research Center

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Friday, August 20, 2004 8:00:47 AM

Rose: Monica's best estimate is 2 1/2 hours per baby. The draft of the data forms were sent to Betty. We should be ready to go. The IRB has just approved us and we can start ASAP.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 17, 2004 8:10 AM
To: Wally Carlo, M.D.
Subject: Re: SUPPORT

Wally
Thanks for your comments. Can you tell me for your pilot secondary - how much nursing time is needed to collect the data? Also, do you have a form?
I sent Betty the protocol.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Neil Finer <nfiner@ucsd.edu>; Betty Hastings <bkh@rti.org>; Michele Walsh <mcw3@cwru.edu>; Wade Rich <wrich@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; Avroy A. Fanaroff, M.D. <aaf2@po.cwru.edu>; Donovan, Edward (DONOVAEF) <edward.donovan@chmcc.org>;
Shahnaz Duara <sduara@miami.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>;
Ken Poole <poo@rti.org>
Sent: Tue Aug 17 09:07:07 2004
Subject: RE: SUPPORT

Dear Neil and All: I agree with the majority and thus, change my vote.
I
think you have presented very good arguments. Let's Roll! Wally

---

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, August 16, 2004 10:16 PM
To: Betty Hastings; Michele Walsh; Wade Rich; Rosemary Higgins; Avroy A. Fanaroff, M.D.; Donovan, Edward (DONOVAEF); Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; Ken Poole
Subject: SUPPORT

Hello Everyone
By now you are probably just as frustrated receiving an email from me as

I
am. We circulated the Re-intubation criteria for the Control infants
with
the question of deleting them.
The vote was 2 against, Shahnaz and Wally, and the rest for. Wally and
Shahnaz are worried about a drift/creep toward the CPAP group if these
are
deleted. I think that this is a very reasonable issue. The initial
concern
is that the re-intubation of such infants is a must, and it occurs after
these infants have already been intubated and received surfactant, and
this
may occur at up to 14 days of age. This is a problem because the average
duration of intubation in the network for the larger strata is around 7
days
(actually 6.28 + 5.14).
As a result, and because the major difference is the early receipt of
surfactant versus CPAP, and the Surfactant infants will be extubated at
lesser criteria, the protocol already sets up the differences in the
group
from birth. The re-intubation criteria essentially force re-intubation
on
infants who have had surfactant, and may have been extubated following
usual
Network practice.
Thus, we could leave these criteria for 7 days as one option, and I
suspect
that there would be little effect on the 24 - 25 week strata, as most
will
still be intubated. However we were desirous of keeping the protocol
simple
and thus have left the criteria for 14 days for all.
The removal of the Re-intubation criteria for the Surfactant Control
Infants
means that from the ventilation point of the study, surfactant infants
who
are extubated are then managed as per unit standards, which is easier.
Will
forcing re-intubation further magnify any differences between the CPAP
and
the Surfactant infants? If it does, is this what we set out to test?
The other trials are also early interventions and we will be compared to
them. As an approach, if the surfactant arm proves to be superior, we
will
not be recommending early surfactant as a therapy combined with specific
re-intubation criteria, at least not as I see this study.
All very longwinded!!
I conclude that the easiest way forward is to minimize complexity, and
remove these criteria in keeping with the majority opinion, and will
recommend this to Rose. In fairness, I will ask that those who do not
feel
that this approach is reasonable, please send your concerns within the
next
48 hours.
After that period, I will ask Betty to modify the protocol with the
removal
of these criteria and hopefully for the final version and so instruct

Betty.
I have already planned site visits for Duke and Detroit, and will be scheduling a visit for Indianapolis.
Be well
Neil

From: Wally Carlo, M.D.
To: Neil Finer
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE:
Date: Friday, August 13, 2004 5:16:46 AM

Neil: Here are my comments on the secondaries.
My ranking is;
1) MRI as long as the consent does not interfere with enrollment in SUPPORT,
2) Bothe gene studies but would prefer cord blood for the both (the surfactant one says first blood).
3) I do not think we should do the PFT because it adds three interviews but if limited to one interview and review of medical care at 18-22 months, I would have less objections.
4) I do not think we should do the inositol unless it is limited to one sample of blood and then only if consent will not interfere with enrollment in SUPPORT.
Sorry for the delay but I just came off service. Wally

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, August 11, 2004 9:09 PM
To: Wally Carlo, M.D.
Subject: Fw:

Hi Wally
Here are the protocols that we need to vote on. I am concerned that the inositol will require too much blood. We have removed the extubation secondary of Carmen Harrera. I believe that Hintz protocol will be a good safety evaluation and we could get a later consent so as not to wear out our welcome with the families. The surfactant and Asthma studies require cord blood.
Please let me know your priorities
Be well
Neil
----- Original Message -----
From: Neil Finer
To: 'Shahnaz Duara' ; Avroy A. Fanaroff, M.D. ; 'Ed Donovan' ; higginsr@mail.nih.gov ; 'Neil Finer' ; 'Wade Rich' ; 'Betty Hastings' ; 'Ken Poole' ; 'Michele'
Sent: Monday, July 19, 2004 11:33 AM

Hello All
Please re-review/ review the attached Secondary protocols for SUPPORT and vote your level of enthusiasm. Rose will need a Yes/No with a 1-5 level of enthusiasm for each 1 being very enthused and 5 being very low enthusiasm. Then rank the studies you have voted Yes on from 1 to 5 or less.

1. Hintz MRI Yes ___ No ____ If Yes Rating 1-5 _____ - Any
Comments_____
2. Schibler – Asthma Genes Yes ___ No ____ If Yes Rating 1-5 _____ - Any
Comments_____
3. Stevens – Pumonary FU Yes ___ No ____ If Yes Rating 1-5 _____ - Any
Comments_____
4. Cotton- Surfactant Genes Yes ___ No ____ If Yes Rating 1-5 _____ - Any
Comments_____
5. Cotton – Inositol Yes ___ No ____ If Yes Rating 1-5 _____ - Any
Comments_____

Overall Ranking of Studies with Yes votes
1. _____
2. _____
3. _____
4. _____
5. _____

On the basis of today's call we will ask Betty to use the Benchmarking forms for PN Steroid use, and to indicate that a HUS is required from day 4 to 21.

Please send your responses to Rose, or just copy everybody with your votes.
Sorry for the additional email clutter. Thanks
Be well
Neil

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Thursday, August 12, 2004 1:32:26 PM

Rose: I would like it for our center. Our people will probably believe more what Ed or Neil say than if only I say it. wally

---

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, August 12, 2004 12:28 PM
To: Abbot Laptook (E-mail); Wally Carlo, M.D.; Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Fanaroff Avroy (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; Michelle Walsh; Neil Finer; Oh William (E-mail); Poole Kenneth (E-mail); Ronald GOldberg; Shahnaz Duara; Shankaran Seetha (E-mail); Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); Walid Salhab (E-mail)
Cc: 'petrie@rti.org'
Subject: SUPPORT

Hi,
As all of you know, Neil Finer and the members of the SUPPORT subcommittee have offered to go to individual network centers for on-site training to address issues which may be unique to your specific site. Please let me know by August 19, 2004 if your site would like to take advantage of this opportunity for additional training for the SUPPORT protocol over and above the training scheduled for September in CIncinnati.

Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(for Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

From:	Wally Carlo, M.D.
To:	Higgins, Rosemary (NIH/NICHD) [E]
Cc:	wrich@ucsd.edu
Subject:	FW:
Date:	Tuesday, August 10, 2004 10:04:39 AM
Attachments:	PILOT STUDY OXYGENATION TRIAL IN ELBW INFANTS revised 5 18 04 NF-2.doc

Rose: Here is the last draft of the O2 pilot. Wade: Could you confirm this is the last draft as I know you made some edits? Wally

---

From: Marsha Sumner
Sent: Tuesday, August 10, 2004 9:06 AM
To: Wally Carlo, M.D.
Subject:

Pilot Study for the Oxygenation Trial in Extremely Low Birth Weight Infants

Abstract

Objective: To determine if infants managed with a higher SpO_2 target (91-95%) for 24 hours during the first week after birth will result in at least a 3% lower SpO_2 than infants managed with a lower saturation target (85-89%).

Study Design: Multicenter, randomized masked trial.

Eligibility Criteria: Subjects will be infants of 24 0/7 to 27 6/7 weeks who are receiving mechanical ventilation on continuous positive pressure during the first week after birth.

Study Intervention: Infants will be randomized to high or low saturation targets and FiO_2 and ventilator settings will be adjusted by clinicians to accomplish the clinically desired saturation targets. Alarm limits will be set at 85 and 95 %. Clinical targets will be within this range. Infants in both groups will be monitored for adverse events including desaturations below 80% and below 85% and for metabolic acidosis (bicarbonate level).

Primary Outcome Measure: Separation of median SpO_2 by at least 3%.

Sample Size Estimate: The number of infants to be enrolled will be determined with RTI's advice.

Statement of problem

Oxygen saturation (SpO_2) targets in infants vary markedly between centers and there is no consensus on the targets that optimize outcomes. Published acceptable levels of SpO_2 in neonates range from 85 to 98%. Even lower SpO_2 targets have been used in neonates with apparent safety. Keeping SpO_2 targets in the high side of this range may have short term benefits such as prevention of desaturation, vasoconstriction and bronchoconstriction episodes. In addition, in infants with prethreshold retinopathy of prematurity (ROP), progression to threshold ROP may be reduced with higher SpO_2 targets even though ROP increased incidence may be when high SpO_2 targets are used. However, a randomized controlled trial of infants beyond the first month after birth reported that SpO_2 in the high 90s did not improve long term outcomes but worsened pulmonary outcomes. In contrast, there has been concern that keeping low SpO_2 values may result in cerebral palsy and that higher SpO_2 values may prevent neurodevelopmental impairment. A consensus conference on assisted ventilation concluded that blood gas targets do not have to be in the "normal" ranges and that lower than normal SpO_2 targets may be preferable for ventilated patients. However, there is no consensus of optimal SpO_2 targets in neonates. Targeting lower SpO_2 than commonly used currently (90s) may lead to a lower incidence of bronchopulmonary dysplasia and retinopathy of prematurity.

A recent randomized controlled trial targeted SpO_2 between 91 to 94% versus 95 to 98% in preterm infants born at less than 30 weeks of gestational age when they had reached a postmenstrual age of 32 weeks. This large randomized controlled trial reported that there was no

improved growth or neurodevelopment (blindness, cerebral palsy or developmental quotient) by keeping SpO_2 95 to 98%. However, targeting high SpO_2 resulted in a longer period of oxygen supplementation after randomization (40 versus 18 days) and a higher dependence on oxygen supplementation at 36 weeks and after discharge. A study to target high SpO_2 in infants with prethreshold ROP showed that there was a decreased progression to threshold ROP but there was a prolongation of oxygen supplementation and hospitalization with a target of higher SpO_2.

However, these studies have targeted SpO_2 in infants beyond the first month after birth. It is necessary to determine the desired oxygen targets in infants starting in the first days after birth because lung injury, ROP, and other complications due to high or low SpO_2 may start early after birth or take a longer time to develop.

The current pilot study will be a short term study to test the feasibility of aiming for two different targets of SpO_2, one of which is around the lower limit of current practice in many centers (85-89%) and the other on the upper limit (91-95%).

Hypothesis

We hypothesize that relative to infants managed with a higher SpO_2 target (91-95%) for 24 hours during the first week after birth, that the use of a lower SpO_2 (85-89%) will result in lower median saturation by at least 3%.

We hypothesize that relative to infants managed with higher target range (91-95%), the use of a lower SpO_2 (85 to 89%) for 24 hours during the first week after birth will result in:

Secondary hypotheses:

1) an improvement in oxygenation index for infants on a ventilator.

2) no change in $PaCO_2$, bicarbonate, or pH.

3) desaturation below 80% and below 75%

4) no unblinding of the caretakers

Study subjects will be infants of 24 and 0/7 to 27 and 6/7 weeks if they are receiving mechanical ventilation or continuous positive airway pressure. Infants will be stratified into two gestational age strata from 24 0/7 to 25 6/7 weeks and from 26 0/7 to 27 6/7 weeks, obtained by best estimate of gestational age according to the GDB stipulated hierarchy.

Inclusion criteria are as follows:

1) 24 0/7 week to 27 6/7 week

2) Infants receiving CPAP or mechanical ventilation with a > 30% oxygen supplementation.

Exclusion criteria are as follows:

1) Infants outside of the gestational age window at birth or beyond the first week after birth

2) Infants whose parents/legal guardians refuse consent

3) Infants born during the time when the research study personnel are not available.

Rationale/justification

It is still unknown what the optimal $SaPO_2$ targets are for infants during the first week after birth and whether targeting different saturations actually result in distinct ranges of saturations in infants. The approved Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial) of the NICHD Neonatal Research Network will test whether targeting oxygen saturations for a prolonged period results in improvement in important clinical outcomes. The purpose of this pilot study is to determine if during a 24 hour period, targeting different saturation ranges results in different SpO_2 levels in these infants.

Background/previous studies

There is now an emerging body of information that suggests that many of the morbid conditions associated with extreme immaturity are potentiated by an excess of free-radicals occurring in infants who are intrinsically deficient in antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase. During hypoxia, metabolic alterations prime hypoxic cells to produce free oxygen radicals when subsequently exposed to oxygen. Such reperfusion injury, in addition to increasing the production of free oxygen radicals, is associated with other metabolic changes which may produce long lasting harmful effects. Silvers et al reported that a low plasma antioxidant activity at birth in premature infants was an independent risk factor for mortality (1).

Pulmonary oxygen toxicity, through the generation of reactive oxygen/nitrogen species in excess-of antioxidant defenses, is believed to be a major contributor to the development of BPD (2,3,4). For example, the preterm macrophage showed a significant increase in cytokine mRNA and protein after overnight incubation in 95% oxygen compared with cells from term animals. Only macrophages from premature animals had a significant increase in intracellular oxygen radical content, measured by 2', 7'-dichlorofluorescin analysis, after incubation in 95% oxygen. This enhanced inflammatory cytokine response to oxygen has been postulated to be a mechanism involved in the early development of chronic lung disease in premature infants (5). Varsila et al noted that immaturity is the most important factor explaining free radical-mediated pulmonary protein oxidation in premature newborn infants and that oxidation of proteins is related to the development of chronic lung disease (6).

There are a number of prospective randomized trials that have compared the use of room air with 100% oxygen for neonatal resuscitation, and these have reported that infants resuscitated with room air resumed spontaneous breathing faster and required less positive pressure ventilation than infants resuscitated with oxygen (7, 8). Vento et al also demonstrated that that infants resuscitated with oxygen demonstrated long lasting evidence of oxidative stress and activities of superoxide dismutase and catalase in erythrocytes that were 69% and 78% higher, respectively compared with control infants resuscitated with room air at 28 days of postnatal life (9). A recent meta-analysis of room air vs 100% oxygen resuscitation comprising of 1,693 infants in five trials revealed decreased neonatal mortality in infants resuscitated with room air (6 vs 11%, $p<0.005$, OR 0.57, 95% CI 0.40 – 0.81) (10). While these studies described results of mostly

term infants, some infants were premature and the premature infant is known to have decreased antioxidants which would increase their susceptibility to oxygen toxicity. In the only randomized prospective trial to evaluate room air compared with oxygen in preterm infants, Lundstrom et al. resuscitated infants of less than 33 weeks gestation who were randomized to receive either 80% oxygen or room air and noted that 2 hours following delivery, the room air infants had a higher median (interquartile range) cerebral blood flow compared with oxygen resuscitated infants: 15.9 (13.6-21.9) vs 12.2 (10.7-13.8) ml/100 g/minute) (11). They did not find any significant differences in short or long-term outcomes but did note that SpO_2 was lower in the room air infants with values at 5 and 7 minutes of 75% and 80% compared with 92% and 94% in the 80% oxygen group ($p<0.001$). Current monitoring with pulse oximetry using limits of 95 to 96% will result in significant periods wherein the infants actual PaO_2 may increase to very high levels, as there are rapid increases in PaO_2 with very small increments in SpO_2 at this plateau portion of the hemoglobin dissociation curve.

Tin et al retrospectively reviewed outcomes for infants admitted to various neonatal intensive care units in northern England from 1990 to 1994 and managed with lower (70-90%) or higher SpO_2 ranges (88%-98%) (12). They reported that infants who were managed for at least the first 8 weeks of life with SpO_2s from 88-98% developed retinopathy of prematurity severe enough to be treated with cryotherapy four times as often as infants managed with the lower SpO_2 ranges. Infants managed with the lower SpO_2 ranges did not have increased risk of mortality or neurodevelopmental impairment. Bancalari et al. using transcutaneous oxygen monitoring were able to show that infants who received continuous monitoring had a similar incidence of ROP to

infants who were monitored by intermittent sampling had similar incidences of ROP, however for subgroup of infants ≥ 1100gm, there was a decrease in the incidence of ROP (13). The STOP-ROP trial randomized infants with already established pre-threshold retinopathy and an SpO_2 less than 94% to two ranges of SpO_2 (89% to 94% versus 96% to 99%), for at least 2 weeks and until both eyes were at study endpoints. The higher range of SpO_2 was associated with a non-significant decrease in the progression of ROP, but was associated with a greater need for oxygen and more exacerbations of BPD (14).

Chow et al reported their observations following the institution in 1993 of a detailed oxygen management policy that included strict guidelines in the practices of increasing and weaning of fraction of inspired oxygen (FIO_2) and the monitoring of oxygen saturation parameters in the delivery room, during in-house transport of infants to the NICU, and throughout hospitalization (15). The main objectives were to avoid hyperoxia and repeated episodes of hypoxia-hyperoxia in very low birth weight infants. Their approach was initiated at birth, and included the avoidance of repeated increases and decreases of the FIO2, and a change in previously used alarm limits. They reported that following the implementation of these new management strategies that the incidence of ROP Grades 3 to 4 decreased consistently in a 5-year period from 12.5% in 1997 to 2.5% in 2001 and that the need for ROP laser treatment decreased from 4.5% in 1997 to 0% in the last 3 years. They adopted an SpO_2 range of 85% to 95% for infants > 32 weeks gestation at birth, and a range of 85% to 93% for infants < 32 weeks. In addition some of their faculty used a range of 83% to 93%. This study did not provide any prospective values of the actual SpO_2 ranges that were actually achieved in their infants, and thus it is uncertain

whether their observed reductions in ROP were related to the altered SpO_2 changes, or to overall changes in management over the period of the study. While these observations are encouraging, the authors did not report the complete neurodevelopmental outcomes for the infants cared for during the period of the new oxygen guidelines, and in the absence of contemporaneous controls, these results cannot be considered as proof that the SpO_2 ranges used by this group are beneficial in terms of significant longer -term neurodevelopmental outcomes.

The most recent trial conducted compared SpO_2 ranges of 91% - 94% versus 95% - 98% in 358 infants of less than 30 weeks who remained oxygen dependent at 32 weeks. The primary outcomes were growth and neurodevelopmental measures at a corrected age of 12 months. The high-saturation group received oxygen for a longer period after randomization (median, 40 days vs. 18 days; $P<0.001$) and had a significantly higher rate of dependence on supplemental oxygen at 36 weeks of postmenstrual age and a significantly higher frequency of home-based oxygen therapy but resulted in an increased duration of oxygen supplementation (16). They reported that additional oxygen supplementation did not improve survival, growth, or the occurrence of cerebral palsy at 18 to 24 months.

There is a need to determine that the use of altered pulse oximeters lead to a difference of actual saturations between the groups but will not lead to inadvertent unblinding of the primary care taker. There is a need to also determine that the use of common alarm limits will not interfere with achievement of the separation of SpO_2 values. The entire range of displayed SpO_2 values is altered either high or low from 85% to 95%. The maximum difference between the high and low

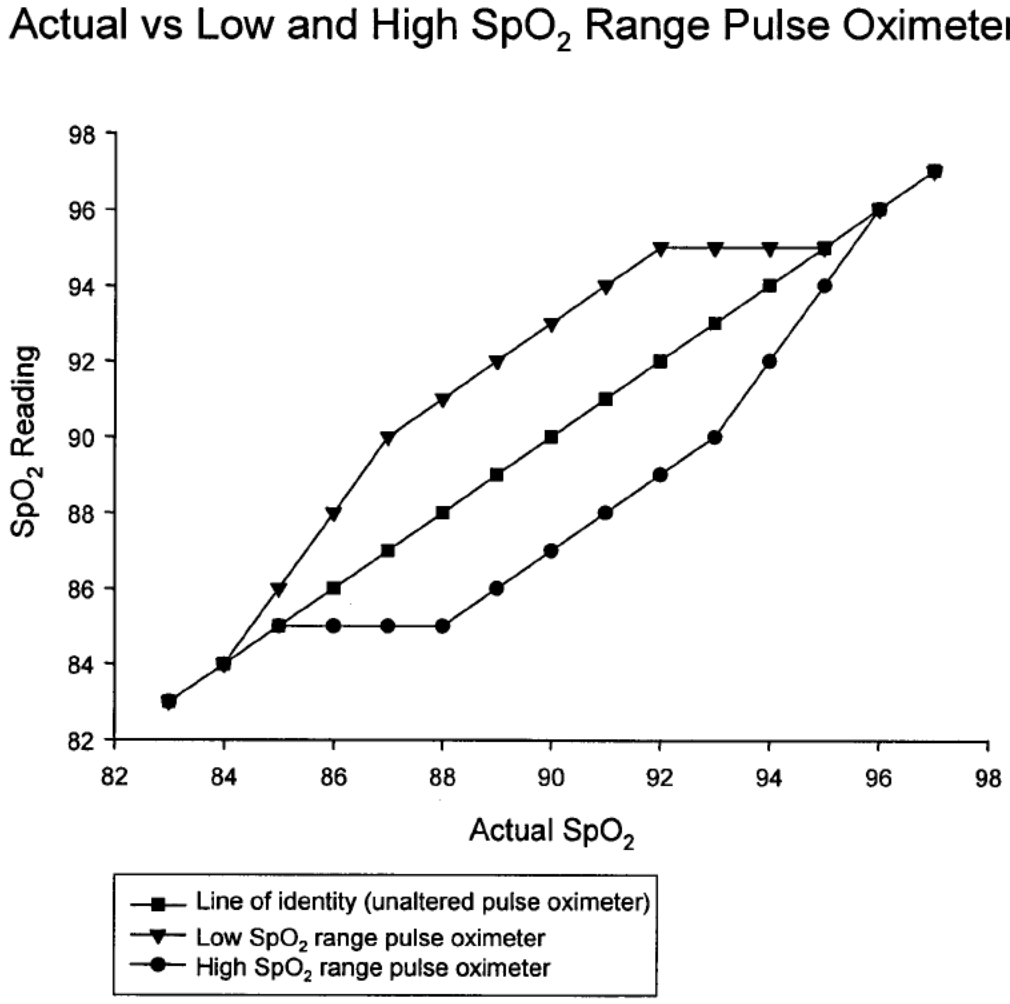
pulse oximeters will be at the center of the target range, approximately 90% as a displayed value. However, the alarm settings will be at the more usual 85% and 95%. Thus it will be important to determine if the use of these altered pulse oximeters results in an actual separation of true SpO_2 values. This calculation will be performed by back converting the displayed SpO_2 values using the actual table of altered values for the high and low oximeters.

Methods/procedures

Description of the study:

This will be a randomized pilot study, stratified by gestational age and masked to clinicians and investigators. Infants will be randomized during the first week after birth to a low SpO_2 target (85-89%) versus a high SpO_2 (91-95%). The different targeting will be achieved with pulse oximeters that have been electronically altered to provide a varied target output as described below. The pulse oximeters will have unique identifying labels. The oximeters specified in the randomization will be identified by a unique number which will match the number of the pulse oximeter assigned to that infant. An identification code will be maintained by the PI/site coordinator should identification be required for patient safety. RTI will work with Massimo to insure that the pulse oximeters are labeled with unique identifiers whose code will identify the actual range of the individual pulse oximeter. An informed consent will be obtained from the parents.

The pulse oximeters will have an averaging time of 12 seconds and an alarm delay of 12 seconds with a second level alarm for SpO_2's < 80%. The target range will be 88-92% and the alarm limits will be 85% to 95% as noted above. This the actual alarms will be activated when the averaged SpO_2 is 84% or 96%, and these values are actual, not altered as noted in the above diagram.



Wide Target ± 1 Alarm	CRT Output Target	Actual Target	CRT Output Alarms	Actual Alarms
Low SpO_2 range group	88-92%	86-89%	85-95%	84-96%
High SpO_2 range group	88-92%	91-94%	85-95%	84-96%

This system will allow maintenance of masking while at the same time provide a safe margin for alarms to function at the currently used levels.

Randomization will be stratified according to gestational age from 24 0/7 to 25 6/7 and 26 0/7 to 27 6/7 weeks of gestation.

Study population:

The study population will be obtained by convenience sampling of eligible infants who meet inclusion/exclusion criteria.

Study intervention:

The intervention will be keeping saturations in the low or high targets as described below. All clinical and research personnel will be kept masked to the specific alteration to the monitor used although they will all be aware that an altered output saturation is being used on the patients.

Analysis plan/Sample size estimate:

The primary analysis will be analysis of the continuous outcome of oxygenation index. Infants weaned off the ventilator and CPAP will be considered to have a mean airway pressure of zero, and thus, an oxygen index of zero.

The sample size estimate will be determined in consultation with RTI. The sample size estimate will be based on the median of SpO_2 of the two groups of at least three, using a dichotomous analysis.

Available population:

The available population will be over 100 patients per month and completion of the study should be between one and three months depending upon the number of centers doing the pilot study.

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From: Susan Hintz
To: neil finer
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: neuroimaging and SUPPORT
Date: Monday, July 26, 2004 1:16:53 PM

Hi Neil and Rose,

Just re-looping with you both about the neuroimaging component to SUPPORT. I know there are numerous complexities to the project (especially fiscal), so I appreciate the difficulties we face.

1) Ultrasound - I think **all** centers should be able to perform timed ultrasounds at 7-14 days and at 35-40 weeks. I would expect that all centers should already be performing ultrasounds at these times (i.e. Neuroimaging Practice Parameter guidelines). These data alone would be extremely valuable, and would at least meet the objective of having a neuroimaging safety arm for SUPPORT. We could also still create comparative neurodevelopmental predictive models just with the ultrasound data (factors alone vs. early US+factors vs. late US+factors vs. both US+factors), even if few centers are able to participate in the MRI portion of the project.
- **Question**: Is there a way to incorporate timed ultrasounds in the SUPPORT protocol itself, and create a SUPPORT protocol data sheet for the cranial US data?

2) MRI - We should get a better idea of which centers would be able to partcipate in the MRI portion as we get responses to the questionnaire that Betty Hastings recently sent out. I think it will be a great success if even a few centers could participate - it would probably be the largest number of near-term MRI's in extremely preterm infants in a single study! Also, if we focus on the centers that are already doing routine MRIs, or plan to, it will be less of a financial burden.
- **Questions**: Would there be funding for a center or two that is VERY motivated to do the MRIs? Also, what do you suggest with respect to consents? If the ultrasounds were considered standard of care, perhaps we should just have a second consent only for the MRI - then sedation could be "rolled into" the MRI procedure for centers that require it?

3) DTI - I will put together the ancillary proposal for the DTI portion. I suspect there will be limited ability/interest in this portion, but again, we should be enthusiastic with ANY interest as there are very limited data on this modality in the extremely preterm population. I am also aware of the additional fiscal challenges that this part of the project might pose. We can talk about this at greater length in the near future.

Thanks again for your help and support (no pun intended!) -

Susan

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